

The Indian Physician

VOL. VIII NO 1

JANUARY 1949

WHOLE NO 85

Original Contributions

PEPTIC ULCER

by

DR V M KAIKINI, BA, FRCS (Edn)

Peptic Ulcer is a very common disease and is more common in the Deccan and Madras Presidency than in Gujarat and Northern India. Many etiological factors like local irritation, auto digestion, oral infection, etc., have been put forward as being responsible for the genesis of the ulcer. But it can be proved that the most important etiological factor is the neurogenic factor. In this the sympathetic and the parasympathetic nerves play the most important role. Due to certain abnormal stimuli from the vegetative nervous centre in the cortex of the brain, the vagus is overstimulated giving rise to vagotonic condition, thus disturbing "the duodenal reflex". The resulting hyperchlorhydria and pylorospasm give rise to the formation of peptic ulcer. But even highly potent gastric juice will not produce peptic ulcer without the existence of predisposing factors, like emotional upsets, giving rise to localized circulatory disturbances, prolonged gastric retention and excessive and prolonged gastric secretion and also other factors, including excessive use of alcohol, tobacco, food irritants, etc.

Gastric ulcer is much less common than duodenal ulcer. Out of about 600 cases of peptic ulcer seen by me only 12 were of gastric ulcer and the rest were duodenal. Out of the 187 cases of peptic ulcer operated on by me, only two were for gastric ulcer and 185 for duodenal ulcer.

Hunger pain and its clock-worklike regularity and variation according to season, emotional changes, etc., are typical characteristics of duodenal ulcer. In gastric ulcer pain occurs soon after food and symptoms of gastritis are present.

The best treatment for peptic ulcer is surgical. But no case should be operated on until sufficient trial has been given to medical treatment. Whatever may be the drugs that are used, the chief aim must be to reduce the acidity and to get rid of pylorospasm. Diet and other habits must be well regulated. If medical treatment does not give relief after a definite trial surgery must be resorted to. Gastro-jejunostomy and partial gastrectomy are the two methods which are commonly used. Partial gastrectomy gives the best results. It is not a formidable operation and with proper pre-and post-operative precautions the mortality is very low and the results are good.

A Paper read before 78th meeting of the Seth G. S. Medical College Staff Society on 10th March 1948, with Dr R. G. Dhayagude in the Chair

The Indian Physician, January 1949

Out of the 170 cases of gastro-jejunostomy done by me the mortality was 7, 8 9% There were two cases of jejunal ulcer In the 8 cases of partial gastrectomy that I did for duodenal ulcer there was no death

In the Western countries the surgeons always remove the appendix when doing gastro-jejunostomy operation. Here I find that the appendix is rarely affected in people suffering from duodenal ulcer and only in two cases I removed the appendix. In other cases the patients were never found to be suffering from lesion of the appendix

KALA-AZAR : REPORT OF A CASE OF LOCAL ORIGIN

by

DR P RAGHVAN, MD

The present case of Kala-azar is reported because of its indigenous origin, in a boy of eighteen, who was born and has been staying since then in Bombay

The city and province of Bombay have been regarded as a non-endemic or 'dry' area for Kala-azar and except for a single case report by Row and Patkar, there have been no reports of cases of Kala-azar from Bombay. The cases of Kala-azar so far seen and reported from Bombay have been imported from Bengal, Assam or United Provinces. As the subject of the case under report has been in Bombay and the maximum distance he had travelled was upto Bassein (a distance of 40 miles from Bombay) it was considered to be of sufficient interest to justify the case being presented before the Staff Society

Case Report

Charles Serrao, aged eighteen years, unmarried Christian male, an assistant in a book binders' shop, was admitted on the 13th April 1948 for irregularly intermittent pyrexia, progressively increasing weakness, and constant dull aching pain in the left hypochondrium, of 45 days duration

He had been healthy upto the time of his illness 45 days ago and denied history of any previous illness

His personal history was non-contributory. He had been twice in the past year to Bassein, where he had stayed for a few hours each time. His permanent residence was in a hut (with mud walls reinforced with bamboo sticks) in Wadala village, a settlement in the north of the City of Bombay. The family history was non-contributory. There was no history of fever in any members of the family

Physical examination on admission revealed a lean, anaemic looking boy weighing 99 lbs. Temperature was 97°F, pulse 90 per minute and respirations were 20 per minute. Excepting obvious pallor of the skin, mucous membranes, lips, and nails no abnormal physical signs were noticed on general examination. His cardio-respiratory and nervous systems revealed nothing abnormal. The spleen was enlarged 4 inches below the costal margin and the liver was enlarged 1 inch below the costal margin

On investigation the following findings were noted —

Urine — No abnormal constituents were found

Stools — Few ova of *ascaris lumbricoides* and whipworm were detected

Blood — Total erythrocytes — 3,160,000 per c m m

Hb = 7.6 grms %

Total leucocytes = 4,950 per c m m

Differential count = Neutrophils 85%

The Indian Physician, January 1949

Eosinophiles 13% Monocytes 3% Lymphocytes 49%
Moderate anisocytosis, poikilocytosis and hypochromia
were noted

Napiers Aldehyde reaction was strongly positive

Sternal-marrow smears—showed presence of Leishman-
donovan bodies

Culture of sternal marrow material showed a growth of
leptomonas form of *Leishmania donovani*

Plasma proteins—Total proteins	7.81 grms	%
Albumin	3.56 grms	%
Globulin	4.25 grms	%

Serum Icteric index 3

Serum Van den Bergh's test —negative

Triple Widal reaction —negative

The patient was afebrile after admission till the 26th April when he had a rise upto 99.6° F which subsided after a few hours. He had again a rise upto 100°F on 29th April.

A diagnosis of Kala-azar was made on the basis of the clinical findings, the positive aldehyde test, the presence of Leishman-donovan bodies in the sternal marrow smears and the presence in culture of leptomonas forms of the *Leishmania donovani*.

He was treated with 5 grams of antimony gluconate (Stibatim of Glaxo Laboratories) in ten doses of 0.5 gram each. He had a small epistaxis on the 2nd day of treatment which subsided with routine treatment and on the 5th and 6th day of treatment he developed multiple furuncles and fever which were managed with adequate doses of penicillin. He was discharged on 14th May 1948 apparently cured and was advised to take ferrous sulphate and vitamin B complex. Two months later, the spleen was not palpable and the patient had put on some weight, was feeling normal and had resumed his usual work.

Dr S. D. Dalal and I visited subsequently the colony where the patient resided and examined the inmates of the patient's hut and the neighbouring ones. There were only four people who gave a history of fever in the past, and in none of them could we detect a splenic enlargement.

Discussion—Bombay has so far been regarded as being a 'dry' or non-endemic area for Kala-azar. As mentioned in the introduction a case of undoubted indigenous origin was reported in November 1947 by Row and Patkar¹. To the best of our knowledge, the present case is the second one.

Napier² in discussing the epidemiological considerations in transmission and incidence of Kala-azar pointed out that the conditions necessary for the prevalence of Kala-azar in any area are (1) an altitude of less than 2,000 feet, (2) a humid subtropical climate with a range of temperature between 45°F and 100°F, (3) an average annual heavy rainfall and (4) presence of rich alluvial soil. He also pointed out that inadequate sanitary conditions and accumulation of refuse and untidy surroundings and heavy vegetation near residential places increases the liability to Kala-azar. In considering the absence of Kala-azar in Bombay he felt that the lack of rich alluvial soil and pre-

Perhaps it will be not justifiable to assume that Kala-azar exists in an endemic form in Bombay on the basis of these two reports, but the problem warrants further investigation. Investigation of cases of irregularly intermittent and prolonged pyrexia associated with spleno-megaly from the point of view of Kala-azar and an investigation by the public health authorities of the local sandfly are indicated.

Conclusions—A case of Kala-azar of undoubtable local origin, in a boy of eighteen is reported.

The epidemiological factors which determine the presence of Kala-azar in an area are briefly mentioned.

I am grateful to Dr S. D. Dalal for assistance in following up the case and in examining members of the Wadala village and to Prof L. Monteiro (now head of the Dept of Pathology, Topiwala National Medical College) for help rendered in investigation.

REFERENCES

- 1 R. Row & N. A. Patkar. *Ind. Phy.* VI 251 (Nov.) 1947.
 - 2 L. E. Napier. *Ind. Med. Research. Memoirs* No. 4 219: (Feb.) 1920.
-

Clinical Case Reports

CEREBELLAR TUMOUR BY DR A V. BALIGA

A girl aged about 13 years was admitted on 18-1-1948 for (1) Headache—duration 6 months (2) Diminution of vision—2 months

O D P—She noticed for the first time diminution of vision in the right eye nearly three months prior to admission. Since then both the visions were gradually affected. She also gave history of projectile vomits for some days nearly three months prior to admission. She also gave history of giddiness and that on walking the room seemed to rotate round her. She however could not tell the direction of the rotation of the room. There was no history of convulsions of fits.

Personal history	}	nothing of importance.
Past history		
Family history		

Physical Examination

C N S—Higher functions normal

Cranial nerves—Total loss of vision of the right and partial loss of left side

Papilloedema both sides

Complete deafness right ear due to atresia of the external auditory meatus

Motor System—

Tone	}	diminished in all the extremities
Power		
Co-ordination	}	were normal
Nutrition		

Sensory system—

Nothing abnormal

Rhomberg's sign positive

Reflexes—

Superficial Plantars extensor both sides

Deep reflexes were diminished

Visceral reflexes—

She used to pass urine and stool in bed. Spine was normal

All other systems were normal

Investigations—

Routine examination of the C S Fluid—

Appearance	Clear
Cells	1 cell cmm Lymphocyte
Protein	Normal (0.04%)
Globulin	Slightly increased
Sugar	Normal
Organism	Not detected
Wassermann Test with the C S F	was negative.

Blood picture showed—

Total number of Red B Cells 4.1 million cmm.

Total number of W. B Cells 7600 cmm

The B P was 96.60 mm of Hg

Stools were normal.

Special investigations—

Plain X-Ray of the skull—normal.

She was afebrile throughout her stay in the hospital On 2-2-1948 she suddenly expired

A discussion followed in which several members took part and a tentative diagnosis of a cerebellar tumour was arrived at

AUTOPSY NOTE BY DR S N KOTHARE

Central Nervous System

On removing the skull, the brain showed flattening of the gyri On the dorsal aspect of the left cerebellar hemisphere there was a yellowish white firm mass protruding through the brain tissue It was slightly raised above the surface, irregular and firm to feel The floor of the third ventricle was bulging outwards, suggesting increased intraventricular tension and hydrocaephalus Large amount of C S Fluid oozed on removal of the brain through the severed stalk of the hypophysis The dura and meninges were not invaded

A sagittal section showed dilatation of both the lateral ventricles, the third ventricle and the foramen of Munro

A horizontal section passing through the left half of the cerebellum showed an irregular greyish yellow area 5.0 cms \times 4.5 cms In some places it had a well defined outline, in others it showed tendency to infiltrate insensibly into the surrounding tissue It had approached the dorsal aspect of the pons The medulla was unaffected

SECTION-REPORT

Brain—Showed the structure of a tuberculoma with necrosis, giant cells, epithelioid cells, etc Typical tubercle follicles were also seen

N B—Other systems were not examined as it was a partial post-mortem

INTRACRANIAL TUMOUR BY DR A V BALIGA

A male aged about 22 years admitted on 7-2-1948 for (1) Headache (2) Diminution of vision (3) Giddiness—duration 1 month

O D P—He gave history of exposure 4 months prior to admission followed a month later by a sore on the penis He was then treated for the same A month and a half ago he started getting severe headache in the right fronto-parietal region It was continuous and had resulted in loss of sleep He later noticed diminution of vision commencing first in the left eye and then involving both the eyes A few days prior to admission he started getting sore throat and joint pains

Personal habits

Past illnesses

Family history

} nothing of importance

Physical Examination

C N S—Higher functions—normal

Cranial nerves—Impairment of vision both sides Ophthalmoscopic examination showed oedema of both the optic nerve heads and haemorrhages round about the discs Vision right eye 6/8 and left eye 6/20

The right abducent nerve showed paralysis Other cranial nerves were normal

Motor system

Sensory system

} Normal

Reflexes—Superficial { Abdominal absent on the left side
 Deep Jerks—Biceps, Triceps Knee All absent on both sides
 Ankle Sluggish both sides
 Visceral reflexes normal
 Astereognosis left hand
 All other systems were normal
 His B P was 120/85 mm of Hg
 Investigations C S Fluid routine examination
 Pressure—fluid under pressure (not measured)
 Appearance—clear
 Cells—2 cells per cmm (Lymphocytes) and an occasional
 R B Cell seen
 Protein—within normal range
 Globulin—slightly increased
 Sugar normal
 Organisms—not detected
 Wassermann Test with the C S F was negative
 Blood picture showed—
 Total R B C 4.2 millions per cmm
 Haemoglobin—70%
 C I —0.89
 Total W B C 8,000/cmm
 Kahn test with serum was Positive (++)
 Urine Examination—Nothing abnormal detected
 Special Investigation—
 Plain X Ray of the skull Erosion of the anterior clinoid
 process
 Ventriculography Both the lateral ventricles were
 dilated
 The posterior horn of the right ventricle not shown
 The 3rd and the 4th ventricles not visualised

Clinical diagnosis—

Tumour in the right fronto—parietal region

He was operated upon on 3-3-1948 and expired on 4-8-1948

During his stay in this hospital he was afebrile for the 1st fortnight, later on he developed intermittent type of pyrexia

Dr Athale did not agree with Dr Bahga's diagnosis because of the marked dilatation of the right lateral ventricle. He suggested that it may be a tumour somewhere in the region of the mid-brain. Dr M J Shah agreed with Dr Bahga's clinical diagnosis

AUTOPSY NOTES BY DR S N KOTHARE

Central Nervous System

On reflecting the scalp, the temporal bone was seen separated due to the operative procedure. On removing the skull cap the dura was found torn and a large part of the brain was found lacerated and herniated. The cerebellum was found to be firmly adherent to the dura in the posterior cranial fossa and tumour tissue could be made out on the inner side of the dura. The cerebellum got lacerated whilst separating it from the dura and a firm mass could be felt in its substance.

Right temporal, parietal and frontal lobes showed extensive haemorrhages both on the surface as well as in the substance.

A horizontal section passing through the cerebral hemispheres showed extensive haemorrhages in the cortex and the white matter of the right frontal and parietal lobes. No tumour could be detected in these lobes. There was haemorrhage into the right lateral ventricle. The other anatomical structures were quite normal. The lateral ventricles showed dilation. Section passing through the cerebellum showed an extensive greyish yellow coloured tissue involving practically the whole of its left half. This area was well circumscribed from the rest of the cerebellum and was 3.5 cms in diameter. It had extended to the dorsal aspect of the cerebellum resulting in firm adhesions between the tentorium cerebelli and the cerebellum itself.

SECTION-REPORTS

Brain—Sections showed the structure of a tuberculoma, with areas of caseation, epithelioid cells and many giant cells.

Dura—Also showed typical tubercular follicles.

N B—Other systems were not examined as it was a partial post-mortem.

Continued from page 26

The second of these is freedom of social action in what he deems to be the interests of his patient. Much modern therapy is, in fact, social or has social implications, and the doctor constantly finds it necessary to seek for a patient rest, a change of work, an improved material environment or some other social privilege.

The third of these is freedom of expression on professional matters. The doctor must be free to speak and write as he thinks fit, not only on more narrowly clinical subjects but on all those other aspects of life which the march of social medicine is showing to be parts of the sum total of man's well-being. Only by absolute freedom of interchange of ideas can medicine grow and fulfill itself.—The Medical Press, Feb 11, 1948

Critical Notes and Abstracts

THE PRINCIPLES OF B C G VACCINATION (Arvid J Wallgren; Stockholm, Sweden, *The Lancet*, February 14, 1948, 1 237-239)

Experimental research work and clinical experience have shown that the first tuberculous infection confers an increased resistance against subsequent infections. This resistance is due to specific immunity. In addition to the specific immunity there is in man a non-specific natural resistance. In the long run the course of tuberculous infection is determined more by non-specific natural resistance than by specific immunity.

To be adequate, B C G vaccination must not consist solely in vaccination, the vaccinated persons must be repeatedly tuberculin-tested and protected against exposure to infection by tubercle bacilli until they become tuberculin-positive. Nothing is gained by B C G vaccinating tuberculin-positive persons, and before B C G vaccination the person should be proved to be tuberculin-negative. Even so, he may be in the incubation stage of an infection with tuberculosis.

Where a person is known to have been recently exposed to tuberculosis, B C G vaccination should be postponed until at least six weeks after the date of exposure, and should then be done only if the tuberculin test is still negative. (There is no danger in B C G vaccinating persons already infected, but it confuses the interpretation of results.)

The duration of tuberculin sensitivity produced by B C G is very variable—from less than two years to more than ten. The longer it lasts, the more likely is it that a sub-clinical infection with tuberculosis has been acquired. In practice immunity is held to last as long as the tuberculin test is positive. If a tuberculin-positive person becomes tuberculin negative, he should be revaccinated with B C G. Experience has shown that there is no danger in vaccinating an already infected child, but it should be avoided to prevent misinterpretation of the value of the vaccination.

World opinion is that B C G bacilli cannot produce progressive tuberculosis in man and that a vaccine prepared from these bacilli may be used without danger.

At present three different parenteral methods of vaccination are used: intradermal infection, multiple puncture, and scarification. All three, when successful, produce tuberculin sensitivity. Intradermal injection has been largely used in Scandinavia and has the advantage of being exactly measurable.

There are few carefully controlled studies on the effectiveness of B C G vaccine. I will cite three of the most recent.

Hyge (1947) has described an interesting epidemic of tuberculosis in a Scandinavian school for girls aged 12-18 years. Before exposure to infection 105 pupils were tuberculin-positive, 106 had been B C G vaccinated, and 94 were tuberculin negative. The exposure lasted two months. Of the 105 tuberculin positive girls only 2 fell ill, with mild pulmonary tuberculosis, of the 106 B C G-vaccinated girls 2 acquired pulmonary tuberculosis, but of the 94 tuberculin-negative girls 41 acquired tuberculosis. The morbidity rates in the three groups were 1.9%, 1.9%, and 43.6% respectively.

In the U S A in 1935-38 Arosen and Palmer (1946) vaccinated 1550 tuberculin-negative Indians. As a control group they injected salt solution in 1457 tuberculin-negative Indians from the same place and of the same ages. Annual follow-up examinations showed that the two groups were exposed to virulent infection to the same extent. Deaths from tuberculosis numbered 4 among the vaccinated Indians and 28 among the unvaccinated. The total incidence of tuberculosis was 40 in the vaccinated group and 185 in the unvaccinated.

Ferguson (1946) of Saskatchewan, reported the incidence of tuberculosis among nurses and sanatorium employees in 1934-43. Of 1005 B C G vaccinated nurses in general hospitals 9 (0.9%) acquired tuberculosis, whereas of 759 unvaccinated tuberculin-negative nurses 29 (3.8%) acquired tuberculosis, i.e., about four times as many. This difference between the two groups is also pronounced among graduate nurses and nurse assistants in sanatoria: of 203 vaccinated 5 (2.7%) acquired tuberculosis, whereas of 113 unvaccinated 18 (15.9%) did so.

NITROGEN MUSTARDS IN THE TREATMENT OF HODGKIN'S DISEASE AND LYMPHOSARCOMA (Milton Sherry, M.D., Baltimore, M.D., Southern Medical Journal, February 1948, 41:118-129)

With advent of World War II, research on war gases was resumed. It was appreciated early that the mustards were not only contact vesicants but following absorption could exert cytotoxic actions on variety of tissues. Furthermore, cellular susceptibility to these compounds appear to be related in a general way to the degree of proliferative activity. Studies have revealed a type of action in cells which can be likened to no other chemical agents, but which resembles in many ways that of X-rays except that, so far as we know, the mustards possess no type of radio-activity.

The marked effects of the mustards upon lymphoid tissue coupled with the finding that actively proliferating cells are selectively vulnerable to the cytotoxic action of the mustards suggested the therapeutic use of these compounds in the treatment of neoplasms of lymphoid tissue. Nitrogen mustards in the form of their hydrochloride salts are water soluble crystalline compounds which can be readily dissolved in sterile saline for intravenous administration. The committee on Growth of the National Research Council has received to date over fifteen hundred case reports upon patients treated with nitrogen mustard. The results of this co-operative study will be analyzed and reported at some time in the near future.

The nitrogen mustard is supplied by the Committee on Growth of the National Research Council, in treatment units. Each unit consists of four bottles of 10 mg of methyl bisamine hydrochloride in the form of a dry salt. The nitrogen mustards must be administered only by the intravenous route, great caution being observed to prevent extravasation of the solution. The solution was freshly made by adding 10 cc of 0.9% sterile aqueous sodium chloride solution to a sterile glass bottle containing exactly 10 mg of the dry salt. Injection was accomplished within five minutes after preparation of the solution because of the rapid hydrolysis which may occur with consequent loss of efficacy. The standard single dose of 0.1 mg per kg body weight was injected into the rubber tubing of an intravenous infusion set, special attention

being given to assure free and rapid flow of the infusion and rapid injection of the nitrogen mustard solution. It has been suggested by numerous investigators that in no instance should more than 8 mg be administered at one dose. From experimental work in animals the most efficient regimen was found to be 0.1 mg dry salt per kilogram of body weight injected every day for four days. However, we varied this dosage on occasions. Considerable caution was exercised to prevent the solution from touching the skin or mucous membranes of the patient or physician. On one occasion a small amount of the solution escaped subcutaneously in one patient, and immediately thereafter there developed intense redness, pain, and swelling in the area of the vein. This inflammation did not subside for a period of two weeks, but no necrosis or slough resulted.

Clinical Results—We have treated six patients with Hodgkin's disease, two patients with lymphosarcoma, one patient with giant follicular lymphoma, and two patients with melanocarcinoma. The duration of the disease before nitrogen mustard was instituted varied from three months to twelve years. The indication for nitrogen mustard therapy in all our cases except one was either poor response or intolerance to X-ray or because of the fact that the patient's disease had become refractory to irradiation therapy.

We had two excellent responses and three good responses. These were all in patients with Hodgkin's disease. The other patient with Hodgkin's disease who had been ill for twelve years died several months after one course of therapy. The patient with the giant follicular lymphoma had a fair response and all patients with lymphosarcoma and melanocarcinoma were complete failures.

Toxicity—Nausea and vomiting were commonly observed after nitrogen mustard therapy, occurring with one to four hours after injection and lasting as long as twelve hours. On occasions after the second, third, and fourth injections, the gastro-intestinal symptoms were less severe. Many of the patients complained of a metallic bitter taste during the injection. Occasionally the patient complained of feeling flushed. Diarrhea was not observed in any patient in this series. No febrile response was observed following therapy and there were no chills noted. Some institutions report that pyridoxine and/or sedation alleviated some of these effects. Some hospitals have adopted the procedure of applying tourniquets well above the systolic pressure on the thighs and one upper arm during and five minutes after the injection of the mustard. It was hoped that a portion of the bone marrow would be protected by this technic and that possibly the patient could withstand larger doses. Adequate data are not at hand to warrant more than just a suggestion that the procedure of temporary arterial clusion may be useful in protecting part of the bone marrow. The toxic effects of the mustards on the hemopoietic tissues are in some respects merely extensions of the therapeutic effects. Although the chemicals seem to have a selective action on primitive cells and abnormal hematopoiesis in sufficiently large doses, the compounds affect all elements of the bone marrow, producing a decided leukopenia and thrombocytopenia and a moderate normochromic anemia. In our series the most striking effect was noted in the total white count and to a lesser degree in the absolute number of granulocytes. In only one instance were we able

to detect a definite lymphopenia In no instance was there any striking reduction in the platelet count There developed in several of our patients a moderate anemia

In the doses employed there was no evidence of any disturbance in renal or hepatic function, except in one instance where there was disturbance of hepatic function before treatment and there was definite evidence of improvement after the course of therapy was finished. On several of our patients we had to resort to blood transfusions when there was marked drop in the white count. However, there was no evidence of agranulocytosis, and the white cells in all cases returned to normal limits. Recovery from the leukopenias produced by this drug was not influenced favourably or unfavourably by the administration of pentonucleotide, ferrous adenylate, leukocytic extract or folic acid, nor did whole blood transfusions appear to alter the spontaneous recovery observed in our patients.

Clinical status of the nitrogen mustards —In general, these chemicals have the same total effect on lymphoid cells and those of the bone marrow and on the hyperplasia of the reticulum cells in Hodgkin's disease and does irradiation therapy. Whether they have any advantages over the best possible type of irradiation therapy remains to be determined. It has been found that the mustards are capable of producing salutary effects and even therapeutic remissions in patients who have become resistant to roentgen irradiation. It has been reported that some patients who were unresponsive to either irradiation or to nitrogen mustard therapy demonstrated a favourable response when the two agents were used simultaneously. We have had no experience with this type of treatment. As a rule local and immediate systemic reactions would seem to be less severe after nitrogen mustard therapy than after irradiation, and dermatitis due to the latter is avoided. Certainly therapy should prove to be less expensive because no costly equipment is required. It must be emphasized that the margin of safety in the use of nitrogen mustard is quite narrow. The maximum tolerated dose (that which does not cause harmful hemopoietic effects) is usually not much larger than the optimal therapeutic dose.

Other investigators have reported satisfactory response in the treatment of lymphosarcoma and occasionally in chronic leukemia. We have had no experience in the treatment of either the chronic, subacute or acute leukemias, but it is apparent from a study of the reports of other investigators that no salutary effect has been obtained in the treatment of subacute or acute leukemias. Our results in the treatment of giant follicular lymphoma and in two cases of melanocarcinoma were failures. In the treatment of both chronic myeloid and lymphoid leukemia, there have been reported effects similar to those obtained in the use of irradiation therapy with remissions of the same duration. In polycythemia rubra, remission continues three months to eighteen months.

STREPTOMYCIN IN GENITO-URINARY INFECTIONS
(Clarence G. Bandler, Philip R. Roen and Victor J. Malaire, New York, *Jourl. of Urology*, January 1948, 59: 96-110)

An analysis and evaluation of the effects of streptomycin in a series of 15 cases of urologic infection has been made. Although this

is not a statistically significant number, some helpful observations have been made which are herewith summarized

An antibiotic streptomycin is a valuable addition to the presently existing armamentarium of urologists. There are instances where the ordinarily used chemiotherapeutic and antibiotic agents have been inadequate, and wherein streptomycin apparently proved to be life-saving.

Where organisms are susceptible to the action of streptomycin, the urine may be completely sterilized. The failure to correct underlying pathologic lesions, such as obstructive factors, is definitely responsible for the recurrence of infection following streptomycin therapy and may be a factor in the development of bacterial resistance to this antibiotic agent.

In the presence of a foreign body, e.g., calculus, nephrostomy tube, etc., renal infection may be eliminated temporarily by streptomycin where the offending organism is susceptible to this medication. However, this sterilization of the urine is not permanent and there soon is recurrence of the same organisms.

In vitro tests of susceptibility of an organism to streptomycin cannot always be relied upon to determine its effect in the patient. The immunologic response and resistance of the patient, when added to the streptomycin effect may change the entire clinical response to the antibiotic.

In some cases with pronounced febrile reactions, it has been observed that following the administration of streptomycin there has been clinical improvement, despite the fact that bacteria were still present in urine cultures, indicating that streptomycin has been, perhaps, effective in altering the pathogenicity of the organisms. Whether the change is qualitative or quantitative has not been determined.

In non-specific prostatitis it is possible to free the prostatic secretions of pathogenic bacteria for brief periods, however, insofar as the clinical findings and subjective symptoms are concerned, streptomycin does not change the course of this disease entity.

The streptomycin presently available has definite neurotoxic properties. In this series of 15 cases there were 2 cases of toxic labyrinthitis and 1 case of involvement of the left recurrent laryngeal nerve. In a fourth case there was mild and transitory involvement of the facial nerve. This is an incidence of over 25% of toxic reactions in this small series of cases. In view of the potential toxicity of streptomycin, its prophylactic use in urologic surgery should not be indiscriminate.

STREPTOMYCIN IN THE TREATMENT OF INTESTINAL TUBERCULOSIS (N. Markoff, M.D., Schweizerische Medizinische Wochenschrift, April 10, 1948, 329-332)

We have used streptomycin in the treatment of five cases of intestinal tuberculosis. Since our results in these cases have been favourable so far, we are presenting a study of our technique and results.

Various observers have found that after parenteral administration of streptomycin about 2-6% of the drug is excreted via the intestine. Excretion reaches a maximum within the first two hours, and is complete by the end of 24 hours. Streptomycin can also be demonstrated in the peritoneal fluid following parenteral administration.

Oral administration of this drug divided into small doses, may be

advisable in the therapy of intestinal injections, because streptomycin is unchanged by the gastric juice, and there is little absorption from the bowel. Local therapy in the intestine is also satisfactory, if no stronger than a 0.5% solution is used.

Ulcerative and hyperplastic forms of intestinal tuberculosis are commonest in the ileocecal region. It seemed to us worthwhile to try local therapy by means of a high colonic injection of streptomycin solution, inasmuch as such an injection, if properly given, will pass through the ileocecal valve into the distal portion of the ileum. Accordingly, we used solutions of 250 mg. of streptomycin dissolved in 500 cc. of physiologic saline, to which a few drops of tincture of opium had been added. Injections were given daily for 14 to 15 days.

All 5 of the cases in this study received parenteral as well as enteral (local) therapy with streptomycin.

In case the principal involvement is in the lower colon and in the rectum, where proctoscopic study is possible, colonic irrigation with streptomycin should be equally satisfactory. If, on the other hand, the tuberculous lesions are most extensive in the proximal portions of the small intestine as is less likely to be the case, oral or parenteral streptomycin therapy might be considered. No toxic effects would be expected, if streptomycin were given orally, since absorption from the intestinal lumen is minimal. Large doses would have to be given over a long period of time, however, so the cost of oral treatment would be considerable, parenteral therapy might therefore be more advisable because of its greater economy.

Two effects of streptomycin therapy are noted, in intestinal tuberculosis. First, there appears to be a detoxification, with improvement in the general condition, a falling of fever, an improvement of the appetite. Then there is also a favourable influence locally, as manifested by a regression of the peritoneal signs and of the symptoms attributable to ulceration. Roentgenologically the ulcers may be observed to heal. Functional stenosis may also disappear. A normal stool habit is re-established, as is the return of normal stool metabolism.

The injections were well tolerated by our patients. No undesirable local effects followed the treatment. After a few days of therapy, all 5 patients showed a striking symptomatic improvement. This has persisted at least 6 months, in every case.

We have not yet observed a complete cure, however. The roentgenologic changes, too, clear up only incompletely, yet our preliminary results have been so good, particularly in contrast to those obtained by other methods of therapy, that we feel justified in continuing the streptomycin treatment which we have described in this article.

We have observed no untoward side-effects of streptomycin in this group of cases. On the other hand, neither did we notice any amelioration of the existing pulmonary tuberculosis.

PSYCHOTHERAPY OF THE OBESE PATIENT (Henry B. Richardson, MD, New York City, *New York State Journal of Medicine*, December 1, 1947, 47: 2574-1578)

Obesity of the exogenous type in women may be a result of a personality disturbance, the physical expression of which is the accumulation of fat. The obesity is almost invariably accompanied by abnormal craving for food which is associated with a variety of nervous symptoms.

The treatment is psychotherapy. The fundamental drive is a desire of the patient to regain the love and affection which was hers without the asking when she was an infant. This indicates that eating and the accumulation of fat in the obese woman are an integral part of a personality disturbance dating from early childhood.

A number of motives for excessive eating can be elicited, in addition to the appetite. The most frequent complaint is a feeling of emptiness, a boundless void, which can never be filled and is out of proportion to the physiologic needs. Other symptoms such as resentment, guilt, self-depreciation, depression, and anxiety are common.

The therapist must get the essential facts. He wants to know the spontaneous associations between the physical aspects of her illness and the mental and emotional components. He must avoid leading questions although he may guide the patient in lines of thinking. Such an interview is essentially a conversation and should be far removed from the question and answer of a routine medical history. In other words, the therapist must be a good listener and must try to ease the pangs of her tyrannical conscience, or in psychiatric terms to mitigate the harshness of her super-ego.

When the emotional life is allowed to flow in natural channels the compulsive quality of the eating diminishes. The ensuing reduction of weight is an index of an improved adjustment.

The therapist plays his greatest part through the role of interpretation. He should make all these in an oblique, neutral or tentative form and should minimize topics which are damaging to the emotional security and self-esteem of the patient. Most patients require intensive psychotherapy based on a deliberate application of the principles of psychiatry to medical practice. The relationship between emotional factors and eating is shown directly only by means of the spontaneous associations which are made by the patient.

The initiative of the conversation remains with the patient but the direction is supplied by the therapist. The effect of interpretation depends on the doctor-patient relationship which is analogous to the phenomenon transference in psychiatry.

Compulsive behaviour affections of motor or sensory or visceral functions, or any other so-called "neurotic" symptom. These represent a socially approved escape for the disapproved impulse. What is very important to understand is that the individual himself is no more capable of voluntary control of such symptom formation than of the rate of his heart beat. At times every one manifests such neurotic symptoms. They do not represent ill health any more than does the minor impairment of any other biologic system. Many individuals, although they remain productive and creative, exist continuously only at a level of neurotic adjustment. In other words, the struggle within them is never resolved. When the defences break down sufficiently so that neurotic symptoms cause incapacity, a diagnosis of some type of neurotic reaction is justified. Sometimes this may be an acute decompensation such as occurred during the war in combat in previously well integrated individuals. It occurs too, not infrequently, in civilians who are under acute emotional stress. On the other hand, there is the slow cumulative decompensation seen most clearly in the chronic neurotic invalid.

In both acute and gradual decompensation, severe neurotic symptoms are traceable to psychological injury during infancy and early childhood. The personality of every adult bears some scars of emotional injuries in childhood. A deeper scar, resulting from a particularly traumatic event, represents a specially weak spot—an Achilles heel—which is more subject to later damage by an experience in adulthood similar to the one which caused the childhood scar. Under ordinary life situations such weaknesses are not apparent either to the individual or to the observer.

We see wide variations in the type and degree of reactions of different individuals to the same situations. This fact is apparently confusing to many physicians. They recognize very well that a typhoid inoculation may produce a violent reaction in one individual and no reaction in another. Consequently, it should not be surprising that a particularly emotional experience may produce an extremely neurotic reaction in one person but not in another. However, this phenomenon is often interpreted as being faked by the first person, on the basis that it did not produce the same reaction in a second person.

Too many doctors also seem unable to accept the validity of a neurotic illness, perhaps because of the scotoma for this field in their medical education. Since they have been taught that illness is physical, a neurotic illness is a paradox because there may be no physical findings, or the physical findings obviously do not explain the complaints. They may conclude that the problem is psychological but withdraw in the face of ignorance of suitable treatment methods.

The intangibility of psychopathology in contrast to the visual evidence of physical pathology creates a kind of anxiety in some physicians. One of his responses is seen in the over-examination of a neurotic patient. If this process were harmless, there might be less reason for concern. Instead, as a rule, it intensifies and tends to fix the neurosis. Even a minor physical finding can be used by the patient to justify his illness as a "real" (physical) one and enable him to escape the recognition that it is psychological. It should become axiomatic that one cannot compensate for a lack of understanding by making repeated physical or chemical examinations.

There are many approaches to the examination of the personality. Before mental illness can be diagnosed an investigation of the expressions of the mind and emotions is essential. Just as analysis of the urine pathology, an analysis of the emotional products of the mind, e.g., hostility, is an essential examination to reveal pathology of the personality.

Currently physicians rarely inquire about hate or resentment unless the patient forces this on their attention. Even then they are prone to regard these as unrelated to his heart ailment. For instance, deep resentment or hatred towards some close associate is always indicative of serious conflicts within the individual's psychological life and may be reflected in many varied symptoms. Neurotic patients can help themselves in their recovery, but only after the doctor has stepped into their environment and helped them re-establish their equilibrium. The necessity to have the assistance of a second party, the physician, is due to the fact that the neurotic patient's difficulty is beyond his own control. He needs the help of someone in whom he has faith and confidence.

who understands him who will be patient with him and who will explain him to himself Only then can he have the courage or the will power to examine his own psychology and thus aid in his own improvement

FUNDAMENTALS OF PSYCHIATRY FOR THE GENERAL PRACTITIONER—(James H Wall, M.D White Plains, N Y Pennsylvania Medical Journal, March 1948, 51 622-626)

The second World War, like the first, called attention to the many somatic manifestations of anxiety and exhaustion states The symptoms of depression, fatigue, head sensations, palpitation, gastrointestinal symptoms, and tremulousness are similar to the neurotic complaints of patients encountered in civilian practice These patients can frequently be treated successfully by the medical man who has a knowledge of psychiatry

The early ruling out of physical disease, together with the early recognition and diagnosis of an emotional problem or neurosis are important steps in the successful management of the patient suffering from a neurosis If these studies and investigations are drawn out over a prolonged period of time, the patient may become convinced that the neurotic condition is due to some obscure physical defect which is eluding the physician in his search and the patient is unwittingly encouraged to continue the search himself from one physician and clinic to others It is not to be implied that neurotic patients should not have careful physical checkups at intervals just as should other people in the community Psychiatry does teach, however, that in the absence of physical findings, we have methods of examination which furnish the physician with a body of information that enables him to comprehend the structure of the neurosis as clearly as he is able to comprehend the state of a diseased organ of the body

There are guides for studying the development of the personality just as there are guides used in the study of the physical development and present condition of a patient The detailed study of the life setting in which the complaints or symptoms first occurred is of the greatest importance The patient suffering from complaints referable to the heart, such as feelings of pressure, palpitation, and the associated fear of dying, when found to have no physical pathology, must be studied in the light of his concepts of heart trouble Has he had near relatives, friends, or enemies who have died of heart disease? Has he identified himself with such persons? Frequently the explanation of the mechanism of identification is helpful to patients with neurotic complaints referable to the heart Such patients are suggestible and our language must be simple and direct

The psychiatric approach to the study and treatment of patients with organic disease means often the difference between a life of invalidism and incapacity and an ability to carry on with some satisfaction These patients are frequently burdened with needless fears and false conceptions of their condition Sometimes a frank neurotic condition is also present and they profit by being given time to unburden their thoughts about themselves

In turning to a consideration of the more serious psychiatric disorders, I do not wish to burden you with a detailed description of the various main reaction groups such as the manic-depressive and schizo-

phrenic disorders but in our modern teaching increased emphasis is being placed upon the early recognition and treatment of patients who are suffering from these and other more severe or psychotic reactions

The young person who has felt insecure, sensitive, and has gradually begun to withdraw, comes first to the attention of the practitioner. Through advice and guidance, the family and the patient may be taught ways of balancing interests and improving the personality adjustment. These early signs of schizophrenic illness should be recognized, and if the patient is unable to respond to our suggestions and plans, it becomes necessary for us to seek hospital treatment.

We are finding out more about the role that ambition and a goal in life in keeping with one's abilities and capacities plays in promoting and maintaining mental health. We should not force young people into work or careers which do not appeal to them or for which they are not fitted.

The mental hygiene of courtship and marriage should be faced more squarely. These problems are explosive if suppressed or ignored. Youth is coming to a more balanced attitude toward sex and marriage—considering the significance of compatibility, of personality traits, and of the little personality traits, of similar tastes, and ideals, and of the little personal peculiarities of everyday life. This is not accomplished in mid-Victorian prudishness, but in the light of earnest thought, discussion, and good teaching. As professional men, we should encourage such interest in our communities and schools. Certainly many problems that we encounter in mental hospitals could have been prevented, or greatly alleviated, by such courses. We must learn to live with ourselves and our instincts and work at the art of give and take in this fundamental basic relationship of marriage. It is the important fountainhead of security for the whole family and community.

Many serious breakdowns occur in relation to parenthood. We need courses in psychologic adjustment for both parents. Experience as psychiatrists in mental hospitals shows us the tragedy of a personality coming up to this level of adjustment emotionally immature and unprepared. In the field of obstetrics the mechanical and physical aspects of childbearing have reached near perfection, but in many instances the personalities of all involved are neglected. Studies have shown how many intelligent men and women are burdened with superstitious beliefs at this time. These same studies have shown that doctors who take time to teach the parents, to explain and clear up superstitions and false beliefs, can relieve tension and start parents out on a wholesome path of enjoying their children.

From youth and through ensuing decades many human beings are prone to develop emotional disorders characterized by elation or depression—the manic depressive reaction. It is sometimes difficult to differentiate the early symptoms of the depressive reaction from the symptoms of milder or neurotic depressive states. A history of previous attacks should be kept in mind. The depression is usually more profound and the patient cannot be diverted as easily or made to smile as readily. The sleeplessness is more serious and associated with fear and genuine concern. These patients are suicidal and require close observation; they are best treated in mental hospitals. Our shock therapies hasten the recovery from depressive reactions.

During the past fifty years the life span of man has greatly increased, largely as a result of the progress in medicine and the associated sciences. A greater number of people have to encounter the vicissitudes of the climacterium and old age. The climacterium, or change of life, is usually more dramatic in the woman, with the cessation of menses and the passing of fertility. Aging and the other bodily changes are well-known physical factors and should not be minimized, but the emotional factors should receive more attention. These women need something more than physical investigations and measures of treatment. The psychologic forces at work must be understood. They should be encouraged to unburden their feelings of not being loved, or needed, the worry over financial security, the depressive notions, and the fear of death. The same may be said of men.

The mental reactions due to cerebral arteriosclerosis and senile atrophy of the brain are associated with emotional factors as well as with the social and economic condition of the patient. Anxiety has a great deal to do with incapacitating people of this age group with degrees of sclerosis and senile changes that otherwise might have been endured. Thought should be given to building up a social, recreational, and health program for the aged people in our communities. Apparently more and more people will live to the age of sclerosis and senility, and we should do all we can to alleviate their anxiety through careful attention to their physical health and by encouraging suitable programs of activity for those who retire.

Busy practitioners everywhere can find much in psychiatry that is helpful to their patients. Here is a real opportunity for psychiatry and general medicine to pool their knowledge and experience, to work together for the benefit of the sick and troubled in our communities.

THE TREATMENT OF DEAFNESS WITH VITAMINS AND AMINO ACIDS (Merrill W. Michels, M.D. Oakland, California, Permanente Foundation Medical Bulletin, November 1947, 5 124-129)

There is insufficient realization of the high incidence of hearing impairment in the general population. Spot surveys with the audiometer have indicated that approximately half of the people in the United States have some loss of hearing.

This study was prompted by a recent report of a new method in the treatment of acoustic disorders utilizing high dosages of selected vitamins and amino acids. Hirschfeld et al. published an account of this method which was so uniformly favorable as to be a challenge. Hence with some degree of scepticism, partial reduplication was performed to evaluate independently this mode of treatment.

Deafness is not caused by any one thing but by a veritable myriad of possible etiologic agents. Among these are the group of hereditary-generative diseases of the cochlea and auditory nerve, syphilis, the extension of inflammatory process of the middle ear, trauma, meningitis, intoxications (lead, quinine, alcohol and tobacco), and focal infection. In certain cases, particularly in people of advancing years vitamin B deficiency seems to be of significance. Arteriosclerosis of the internal auditory artery occurs as a determining factor in many cases of presbycusis. Many of these disease processes have resulted in irreparable and irreversible damage. Therefore, any one method of treatment

which makes no attempt at selection and classification must necessarily be fraught with a high degree of disappointment and failure

In the present study, 31 patients who presented acoustic loss of a clinical degree sufficient to seek investigation were treated. Of these, 21 completed the prescribed regimen and returned for follow-up examinations. The group consisted of 17 cases with nerve deafness and 4 with otosclerosis.

The treatment consisted of six intramuscular injections of 2 cc each of Amritol* (Walker) administered over a two-week period. This was accompanied by oral administration of a capsule of Hyvanol (Walker) three times a day. After the first two weeks of treatment, recheck audiograms were made. Some patients were given further parenteral injections of Amritol 2 cc twice a week for two weeks in addition to the oral capsules. Others received adjunctant oral therapy for added periods.

Of the 21 patients who completed treatment, 7 showed definite clinical improvement of sufficient degree to be noted. Five showed slight improvement and 9 showed no change. Some showed only a unilateral gain. The elevation of acoustic function from a low level to a higher plate but still depressed below the 80 decibel line does not give the patient satisfactory hearing. Tinnitus which was a salient complaint in 18 patients was improved significantly or cured in 11 and this usually paralleled improved hearing.

From this study it appears that this therapy does have an apparent beneficial effect on acoustic function in certain individuals. It is anticipated from the observations made that the improvement in acoustic function and rehabilitation may remain fairly stationary.

* Amritol is described as a sterile solution of four pure synthetic vitamin B-complex factors in combination with specific amino acids, choline and urea, in a water-propylene glycol vehicle. Each cubic centimeter contains thiamine hydrochloride 10 mg, riboflavin 2 mg, pyridoxine hydrochloride 5 mg, niacinamide 40 mg, histidine monohydrochloride (1) 20 mg, methionine (dl) 15 mg, tryptophane (dl) 10 mg, choline dihydrogen citrate 10 mg and urea 0.2 Gm, preserved with 0.4% chlorobutanol and 3% benzyl alcohol.

Each Hyvanol capsule contains vitamin A 4000 USP units, vitamin D 400 USP units, thiamine hydrochloride 2 mg, riboflavin 2 mg, pyridoxine hydrochloride 0.1 mg, ascorbic acid 37.5 mg, niacinamide 20 mg, calcium pantothenate 1 mg, cysteine hydrochloride 8 mg, urea 75 mg, tyrosine 60 mg, choline (dihydrogen citrate) 30 mg, glutamic acid 60 mg, liver concentrate 1:20, 25 mg, and dried yeast USP 50 mg.

THE DIAGNOSIS AND TREATMENT OF MENIERE'S SYMPTOM COMPLEX (P. E. Ireland, M.D. Toronto, Ont. Canadian Medical Association Journal, March 1948, 58: 269-278)

Meniere's syndrome, in its characteristic form presents typical recurrent attacks of acute vertigo, tinnitus and decrease in hearing. The first symptom is usually a sudden onset of violent vertigo, but may begin with unilateral deafness or tinnitus. The auditory symptoms may precede the vertiginous attacks by a considerable period.

The attack is usually preceded by some sort of aura. There may be an increase in the tinnitus, increasing deafness or just a fullness in the head. A major attack is characterized by severe vertigo, nausea,

with vomiting present at times. The patient is pale, clammy and lies quite still, terrified that the slightest movement may accentuate the vertigo. The duration may be minutes to many hours. Recovery is rapid but with some persisting unsteadiness. Occasionally mild, persistent vertigo occurs between the major crises.

The diagnosis of Meniere's is based largely on the history. Spontaneous signs of falling in the exaggerated Romberg position with one foot ahead of the other can be tried. Past pointing with eyes closed may be present. Nystagmus rarely present except during an attack. This is constant with any change of position of the head. The other cranial nerves with general tests for co-ordination should be checked to rule out cerebellar or cerebellar-pontine angle tumour.

The importance of knowing which ear is the abnormal one from view point of proposed surgery is obvious. The caloric test showing one labyrinth with a deviation from a normal response is of great value in this localization. The side with the greatest deafness or tinnitus, with the history of falling in this direction, and the spontaneous signs of past pointing to the same side and nystagmus to the opposite side, help to confirm the final localization.

This is not in any way a fatal disease and all the pathologic changes are within the labyrinth, but it can by its persistence and the violence of the attacks reduce the patient to chronic invalidism. The nervous temperament of even the most robust is strained by the mental and physical upsets of the recurrent attacks. Sympathy, encouragement and careful rehabilitation supervision are necessary. Tinnitus often persists in spite of any treatment. The prognosis regarding the cessation of the vertiginous attacks by one or other method of treatment is good. The tendency to spontaneous remission must be kept in mind in regard to the assessment of all treatment. Many cases, even those untreated, seem to run a self-limited course with permanent cessation of all attacks of vertigo.

Treatment Many types of treatment have been postulated indicating probably that none has been too satisfactory. These may be divided into the types of medical and surgical treatment. Surgical treatment is not an absolute assurance of permanent relief of all symptoms. It should be attempted only after the patient's complaints become unbearable and all medical measures have failed.

Medical Treatment The patient is greatly in need of reassurance, as he probably believes he has a brain tumour or some other intractable and fatal intracranial disease. He must be reassured that there is every chance that gradually, and with reasonable certainty, his vertigo can be overcome. A good deal of his discomfort is a profound mental insecurity and sedation is necessary. One of the barbiturates is the most useful drug although hyoscine is perhaps more specific and more effective.

All medical treatments are attempts to control the "hydrops" or the increased fluid pressure level within the membranous labyrinth. Histamine and nicotinic acid probably act directly on the vessel walls in the absorption area in the region of the endolymphatic sac. The sodium ion is supposedly the offending ogre and this is eliminated largely by a strict, salt-free diet and the substitution of $7\frac{1}{2}$ gr or 15 gr of potassium chloride, ammonium chloride or potassium nitrate, three

times daily. It has been suggested that these added salts have their effect only by their diuretic action. The limiting of fluid intake is also essential. This need not be to less than two pints daily.

There have been enough cases reported to have been relieved by removal of foci of infection that this procedure can not be ignored whether the toxic labyrinthitis differs technically from Meniere's or not. Food allergy must also be considered. These are not the easy, skin test variety, but are usually elicited by careful history and personal observation by the patient.

Surgical Treatment The surgical treatment is an attempt to prevent completely the distorted impulses from getting to the cortex with the hope that re-education and so-called compensation will remove the sensation of imbalance.

Resection of the eighth nerve is an operation of little risk in the hands of a competent neuro-surgeon. An attempt may be made to resect the vestibular fibres only, but a certain number of cases have been reported with distortion of hearing that is more troublesome than complete deafness. After compensation has occurred, the main symptom of vertigo is relieved. Tinnitus does persist in a fair number of cases. Also we must remember that Meniere's is probably a bilateral disease and may recur from the other side.

Destruction of the labyrinth is strongly advocated by Hallpike and Cawthorne. All that is necessary is the opening of the semicircular canals with picking up of membranous labyrinth and the application of diathermy. These patients have complete loss of hearing function following operation. We have done 38 of these cases in Toronto. The surgeon trained in fenestration surgery is best suited for this type of operation which should be done under magnification.

I feel that destruction of the labyrinth as a method of treatment has excellent possibilities when surgery becomes necessary. It must be remembered that operative interference is required only in about 10% of all cases treated.

Our Problems . a forum for discussion

RURAL MEDICAL RELIEF

by

S B GADGIL, F.R.C.S

Attempts are being made in all countries to supply qualified medical personnel for rural medical relief. In India, in the near past, a diploma examination called L.M.P. and later called L.C.P.S. was instituted. The course for this diploma was shorter and cheaper and the examination standard was lower than that for the University examination. Those who passed this examination were called Hospital Assistants. The idea of starting such an examination was that these Hospital assistants would practise in small towns and out of the way places where fully qualified men are not available.

The practice of medicine being more an economical than a humanitarian question from the point of view of the medical practitioner, most of these hospital assistants, who were not in government service and could therefore choose their place, settled down to practise in big towns. The Western system of medicine being based on the knowledge of Anatomy, Physiology, Pathology, Physics and Chemistry has proved its superiority to the indigenous systems of medicine, and it has therefore appealed to the majority of the educated population. But there being a scarcity of fully qualified men even in big towns, these hospital assistants were preferred to Ayurvedic and Unani practitioners. These hospital assistants could also afford to give their services at a lower cost than fully qualified practitioners. Our problem of supplying men for rural medical relief was therefore not solved by the creation of this cadre of hospital assistants since they avoided practice in rural areas. Nor has the problem been solved by giving registration certificates to the Unani and Ayurvedic Practitioners nor even to old experienced compounders and dispensers. Even such persons were found to settle down to practise in big towns.

A similar condition of affairs was created in one of the states—San Paulo in America, where in the absence of medical colleges in that state, unqualified men from different countries were given permission to settle in practice, expecting them to go to practise in out of the way places. The authorities were disillusioned in their pious guess. A majority of these unqualified men not only started practice in big towns but a lot of them began to compete with fully qualified doctors by unfair means.

Compulsion is the only remedy for such state of affairs, like conscription in the army when an emergency arises. To create a cadre of men of low medical standard for village work is not fair to the villagers, even when such areas may contain a population of less than 500. To appoint fully qualified men of experience on a permanent footing at a high salary for work in rural areas, where work of a high standard is neither expected nor necessary, would be a drain on government finances.

With these conditions in mind, I propose to submit a plan to achieve rural medical relief with advantages to the conscripted medical man, minimum of compulsion, benefit to the community served and rock bottom expenditure to the state.

We have 4 medical colleges in the Presidency, which produce on an average 100 medical men every six months. They are registrable to practise medicine in all its branches. Many of them have an ambition to gain higher qualifications and have therefore to hold house appointments at these teaching hospitals before they can appear for such higher examinations. It should be made a regulation that those who wish to hold such appointments must have previously worked for six months at a rural government medical centre. Such work has to be certified by the nearest district civil surgeon. The University produces about 30 candidates with post-graduate qualifications every six months. If it is presumed that double this number appear for such examinations it means that about 60 men will have held house appointments at the teaching hospitals. The government can enforce the regulation by a Government Resolution to the effect "That no candidate will be given a house appointment unless he produces a certificate of having done six months' independent work at a Government rural medical relief

centre ” The University can also help by laying down a condition for appearing at a post-graduate medical examination that “Every candidate who wishes to appear for a post-graduate medical examination must produce, along with other necessary certificates, a certificate to the effect that he has done six month’s independent work at a Government rural medical relief centre ”

The Government will have to supply at least about 75 such centres for rural medical relief equipped with a limited number of requisite frequently used drugs, dressings and surgical instruments, and a place of residence for the doctor, his assistant and a peon The existing Dak Bungalows may serve as centres in many places An Honorarium of at least Rs 75 should be paid to the doctor and the others to be paid according to their grade Such expenditure will not bring the cost to more than Rs 200 for each centre

Work at such a centre will encourage a newly qualified man to use his recently acquired knowledge and treat independently various everyday occurring ailments He will be able to get the help of the nearest civil surgeon for difficult cases He may also be able to perform minor operations under local anaesthesia And he will learn village conditions at first hand knowledge Also he will lose practically nothing by being away from his medical college for a period of six months In addition he will learn to appreciate and value the importance of experience and facilities that are usually available at a big hospital in the town The patient from the villages will be spared the inconvenience of going long distances for minor medical or surgical ailments Overcrowding of district hospitals where the staff is usually inadequate, will also be thus avoided The civil surgeon will then have more time to deal with important cases, if only such will now go there from village centres

A report has been submitted to the Faculty of Medicine for approval and submission to the Senate, by seven approved members of the Faculty, most of these members being consulting practitioners, that the rural medical relief under the appellation of social service may be undertaken by a medical graduate, before his registration by the medical council The service is to be of three months of which one month is to be spent at a village centre and 2 months at a college attending lectures in vital statistics, epidemiology and water supply—subjects of which he already has an elementary knowledge I feel that if the plan which I am proposing is followed, the medical graduate will learn to tackle these problems far better by personal experience than by taking a course of lectures No one has ever learnt well either a trade or a profession by attending a course of lectures—personal experience is the only good teacher I do not approve of the idea that a student after qualification should get a Kuchha registration certificate to practise in villages, and after such a work of three months be granted a proper certificate for general practice

Lastly I feel convinced that rural medical relief work for the new medico will serve as a six months’ holiday after the hard work done for his final examination, usefully spent in studying conditions under which villagers live It will necessarily broaden his outlook on life, introduce him to his future life of a citizen and help to build up his character If already married, a six months’ holiday with his wife will give an opportunity to the young women to do social welfare work and learn

to appreciate the good qualities of ordinary womenfolk who have often to live in stramed circumstances The Honorarium of Rs 75 will serve as a scholarship—the amount he will get when he becomes a houseman—and will remind him that he is still a student

There may be a cry for men to serve as housemen at teaching hospitals for the first six months This condition can be relieved either by sending men from provincial services or by taking students who normally would not have had a chance of becoming housemen In any case this is a difficulty which can be easily solved

In the above proposal I have suggested that work at the rural medical relief centre should precede a house appointment However, it may be found that there are many advantages if this work follows a house appointment

[*Editor's Note* —We publish Dr Gadgil's suggestion for inviting discussion from our readers In our opinion the problem of rural health is not simple but complex and bound up with economic, social, and educational problems The type of medical man which our university produces is not suitable for village work. A raw student going to village is likely to do more harm than good to the people there and to himself also We do not see why medical post-graduate students should be conscripted when teachers, engineers, lawyers, social workers, or business men are not conscripted for rural uplift No improvement in rural health is possible without getting the *local population* take interest in their betterment, and this is not possible without *development* of agriculture, animal husbandry, communications, education, housing and sanitation raising the villager's standard of living This work is not for medical students but for the state to plan with the co-operative effort of the local people

The suggestion of the members of the Medical Faculty to the Senate is also futile and will neither solve the problem of rural medical relief nor improve medical education Sometime ago Dr Mahajan had moved a resolution in the Bombay Legislative Council requiring the medical students to do work in rural areas These arm-chair legislators and academicians do not realise the difficulties and the nature of work required in the out-of-way villages To our mind the best solution of the rural health in our province at present is the plan devised by Dr A T W. Simeons, Director of Public Health, Kolhapur State (see, *Indian Medical Gazette* April 1945 p 222) and worked by him with great success for several years in that State This plan, if necessary, with the desired modifications, can be easily adopted for the whole of our Province without any difficulty and with little expense]

Reflections and Aphorisms

THE THREE MEDICAL FREEDOMS

The doctor asks for three primary freedoms
The first of these is freedom to use his skill, knowledge and intelligence on behalf on his patient in the clinical sphere He must be unreservedly at the clinical service of the patient, to investigate, diagnose and treat the patient's disease by whatever means he may decide, traditional or unorthodox, bold or cautious, expensive or cheap

[Continued on page 9]

The Indian Physician

VOL VIII NO 2

FEBRUARY 1949

WHOLE NO 86

Original Contributions

A REVIEW OF PERIPHERAL NERVE INJURIES

by

D K KARANJAWALA M.B.B.S

INTRODUCTION

It is an ill wind that blows nobody any good, and perhaps the greatest single benefit that humanity derives from all warfare is due to the enormous advances in the art and science of surgery

The vast wealth of material that the surgeon comes across, due to lesions both traumatic and inflammatory, in a short space of time improves his clinical acumen and technical skill, beyond measure. He thus becomes more fit for the work of repair which is the aftermath of every war

The veracity of this statement was amply borne out by the occurrence of semi-warfare conditions in Bombay early last year, occasioned by the Naval Mutiny, and by the communal riots later on in the year. As a result of these, our surgeons have become more adept at handling traumatic-surgery-material, as also at organised team work, which consequently has been much better understood

Prior to these events, we had only occasionally seen a bullet-wound and very few lesions (at least in variety) caused by a stab with the knife. But during those hectic days, we saw almost every organ in the body pierced by a bullet or knife, almost every bone broken by it, and lesions of most of the vessels and nerves of both the extremities caused by the same agents

It is from these cases that most of the material for this paper has been taken, and although the results of treatment have not been too gratifying, yet the clinical manifestations exhibited have been worth noting and following up

Pathology of Nerve-injury

After complete section, the cut ends of a nerve retract. If the section is incomplete the cut bundles and fibres retract and form a proximal neurofibroma and a distal glioma, or a lateral neurofibroma. Seddon has given the term Neurotmesis to complete-section

Lloyd Davis states that "when the nerve-trunk has been severely lacerated (*viz* by gunshot injury) the contusion effects are seen under the microscope for a long distance on either end. These areas later go on to necrobiosis and dissolution of nerve tissue. The resulting

A Paper read before 82nd meeting of the Seth G. S. Medical College Staff Society on 12th June 1948 with Dr. A. K. Talwalkar in the chair

pattern of regeneration therefore is more confused and the prognosis correspondingly made worse. To add to these difficulties there is abundant fibrous-tissue reaction in the wounds, which is a natural sequence of the gross contamination and severe infection of such wounds. The toxins or bacteria if not controlled in time may travel in the interior of the nerve trunk and cause an ascending neuritis, which ends up in a wide-spread fibrosis of the connective-tissue framework of the nerve.

Lesions without loss of continuity of the nerve which Seddon calls *axontemesis*, and where the phases of degeneration and attempted regeneration take place inside an intact nerve-sheath are usually caused by an injury giving rise to contusion of the nerve as also by friction of, or traction on the nerve trunk. Here again the amount of connective tissue reaction determines success or failure of regenerative efforts and it often ends up as a fusiform-neuroma.

Lastly when the nature of injury is such that a transient block occurs without loss of continuity of either the axon or its sheaths, or in other words the nerve suffers from a state of concussion (*neuroparva* according to Seddon). The lesion almost always ends up in complete recovery within a week or two.

In our series of nineteen cases, nine suffered complete section of the nerve, six suffered contusion and only four escaped with concussion.

Of the first group, four were severe bullet-wounds with laceration of the surrounding soft parts. Three of them were followed up and ended in failure, the fourth one is not traced. The remaining five were clean cuts by sharp instruments. One of them recovered almost completely, one had a fair amount of regeneration, one refused repair and two ended up in failure.

Of the second group two had fusiform-neuromata, both ended up in failure. One got completely cured, and the remaining three improved enough to regain a fair degree of function.

Of the last group two suffered from *causalgia*, and the other two recovered completely.

Changes in the other tissues occur partly as a result of trauma inflicted but mainly as a result of the nerve-involvement. These changes occur in the tissues to which the terminal nerve fibres are distributed, and are due either to

(a) disuse—which is an inevitable sequel of nerve-block or (b) to irritation of sympathetic and sensory axons which remain intact. These latter changes are known as *trophic*, and sometimes give rise to a clinical entity known as "*Reflex sympathetic dystrophy*". The characteristic changes herein are

- (1) progressive fibrosis of muscle bellies, tendon-sheaths and joint capsules
- (2) degenerative changes in the superficial tissues, and
- (3) porosis of the bones of the hand and foot.

According to Livingston these changes are brought about as follows. "A prolonged bombardment of pain-impulses sets up a vicious circle of reflexes spreading through a pool of many neurone-connections, upward, down-ward and even across the spinal cord, and perhaps reaching as high as the thalamus itself. Because of the summation of nerve-impulses, there is kept alive within such a pool (known

as the Internuncial pool, a constant circling of activity across the synapses involved. Some of the synapses include the sympathetic-motor-neuron-cells in the lateral-horn controlling vasomotor tone and sweat-glands.

Spasm in the articular and venous-end of the capillary loops raises filtration pressure, and oedema and swelling result. Cyanosis and anoxaemia increase capillary permeability and filtration, further augment oedema.

Other synapses involved may be the anterior motor-horn cells, giving rise to skeletal muscle cramps and spasms. Out of the pool also arise augmented stimuli to pain, travelling up the thalamic tract.

Depending on the wide-spread of the pool, the phenomena of pain and sympathetic disturbances are observed far from the injured area in the limb. The afferent pathway is represented as the sensory fibres in the posterior roots since, (according to Livingston after careful review of the evidence) pain bearing fibres do not exist in the sympathetic somatic system. Therefore the abolition of pain in these conditions by severance of the sympathetic pathway is not directly due to any blocking of afferent pain fibres, but to the interruption of the efferent sympathetic pathways leading from the internuncial pool.

Pain is usually the most prominent feature. It may be a most excruciating, deep burning agony that makes the patient wince at the approach of the examining hand and sometimes makes him contemplate suicide.

Ethological Factors

Various types of trauma have been described as giving rise to nerve lesions. They mainly fall into two groups.

- (1) Where the nerve is involved directly by the traumatic agent, and
- (2) Where the nerve gets involved as a sequel to injury of the surrounding tissues.

In the first type the nerve injury is said to be primary and depending on the traumatic agent and its vehemence, there is a section of the nerve as by bullet-wound, stab, etc., or there is laceration caused either by the extraneous agent or by the fragments of the neighbouring broken bone, e.g., median nerve laceration in supracondylar fracture. The other types of primary injuries are crush-injuries blunt or open where the nerve suffers compression or contusion, as also traction injuries which occur in cases of dislocations and fracture-dislocations.

As opposed to the above-mentioned, when the nerve-lesion manifests weeks after the injury due either to friction occurring in a bony groove viz., ulnar-neuritis or by its involvement and late compression in callus or scar-tissue, or a plaster-cast. The injury is said to be secondary.

Lastly if the nerve-involvement occurs years after the primary injury as a result of a gradually increasing deformity causing a stretch or pressure on the nerve as in a case of cubitus-valgus following excision of the capitellum, the injury is said to be delayed.

In our series there was no case of delayed type of injury.

Of the secondary type there were three cases in all. One of them had a fusiform neuroma on the ulnar as a result of friction following fractured elbow. One had medical nerve-causalgia due to involvement

Descent of the motor point was also demonstrated in a case of the radial nerve injuries

Included in the Syndrome of Irritation is a clinical entity known as Causalgia which seems to be due to irritation chiefly of the sympathetic fibres as it mostly affects peripheral nerves rich in these fibres viz, sciatic and median

Ever since Wier Mitchell so vividly described its characteristics as occurring in wounded soldiers in the American Civil War, literature on the subject has been accumulating, and much attention is being paid with particular regard to its causation and treatment

As described on the previous pages, Livingston in his book on "Pain-Mechanism" has given a very graphic account of the probable cause, as also the different clinical varieties and the criteria of treatment

Ulmer and Mayfield have recently published a statistical review of their cases and have clarified and laid emphasis on certain points

James Evans calls this condition, the syndrome of "Reflex Sympathetic dystrophy" and objects to the term "Causalgia" which he says is a misnomer because of the absence of pain in some cases

Apart from the characteristic pain, the changes that occur in other sympathetic disturbances in the extremities are identical, and these therefore have been termed "The Minor Causalgia"

Ulmer points out the two types of Causalgia seen

One where the skin is blue, shiny and bereft of hair, the nails brittle and stunted, and the onset of contractures early

In the other variety the reverse obtains. The skin is flushed and dull, the affected part is warmer and more hirsute and perspires freely

Both these forms are accompanied by an agonising pain of a bursting and burning character, and exquisite tenderness along the nerve-trunk, (more marked in the milder cases). Exacerbations of the pain occur by all forms of physical or emotional stimuli however slight, so much so that the patient does not allow his limb to be washed or even touched. He looks anxious, is taciturn and irritable, loses sleep and appetite. His condition is pitiable in the extreme, as he even contemplates suicide to get rid of his pain

The two types of changes described above are due to a marked vaso-constriction of the affected part in one case as opposed to the vaso-dilation obtained in the other. This fact has been proved conclusively by oscillometric studies, and skin temperature readings

The effect of moisture also varies with the type of vascular disturbance. Thus the vaso-constriction case gets relief by immersing the part in warm water, whereas the other obtains relief by cold water. Fever is also employed as means of temporary relief in the vaso-constriction case. In roentgenograms osteoporosis is more marked in the vaso-dilation type

The alteration of blood flow in these cases does not seem to be responsible for the pain nor are infection and scar-formation of etiologic importance

The diagnosis depends largely on demonstration of relief by procaine block of the sympathetic ganglia innervating the part. The pain initiates a reflex paralysis which is overcome by the block, thus

revealing the exact amount of disability, and thus distinguishing it from other nerve-lesions

Treatment aims at interruption or abolition of the painful impulses passing from the seat of injury With this end in view the following manoeuvres have been tried

- (1) Procaine block of the nerve trunk,
- (2) Neurolysis of the nerve,
- (3) Excision of the affected section with end-to-end suture,
- (4) Section of the posterior roots
- (5) Periarterial sympathectomy
- (6) Procaine block of the lumbar or cervical ganglia
- (7) Sympathetic ganglionectomy
- (8) Chordotomy
- (9) High amputation as a last resort
- (10) Destruction of part of the sensory cortex in cases of phantom projection

Of all these procedures the most effective and therefore most widely practised at present is sympathetic ganglion resection after a trial procaine block. This is the treatment advocated by Ulmer in his paper

He mentions that lack of relief or recurrence of symptoms after sympathectomy are due to incomplete sympathetic denervation which can be detected by the occurrence of local sweating The starch-iodine test is very helpful in locating such spots He therefore says that if this test is positive, it is an indication for a sympathetic resection higher up which must include the supply of the injured segment of the nerve

The two cases in our series were both of the vaso-constriction variety and exhibited typical symptoms One was of the median nerve following compound fracture in fore-arm, and the other was a case of bullet injury of the thigh In neither case was the nerve directly lacerated In both, the wounds healed without sepsis All these facts are in accordance with the usual picture seen

The treatment followed in both was

- (1) Repeated procaine block of the nerve trunk with fleeting relief followed by
- (2) Neurolysis of the affected segment which also in either case failed to give more than very transient relief Block of the sympathetic was thought of but not attempted

The median nerve case left the hospital in a state of desperation and is not heard of to date The sciatic injury somehow got used to the condition Even now he complains of mild burning and formication in the foot and ankle with occasional exacerbations of lancinating pain, his limb is wasted to a shadow of its neighbour But on the whole he is tolerably comfortable and does not desire any further surgery

Diagnosis

Interesting clinical pictures were particularly noted in our three cases of brachial plexus injuries, the most interesting being the case of the patient who got a lesion, as it were of the trunk formed by the 5 and 6 cervical roots distal to the serratus anterior and suprascapular branches The muscles most affected were those supplied by the radial and musculo-cutaneous resulting in utter weakness of flexion

at the elbow and extension at the wrist. Recovery was pretty rapid. The power returning earliest to the pectoralis major and to the latissimus dorsi muscles. The anaesthesia in no part of the arm was complete but there was hypoaesthesia on the lateral aspect of the fore-arm and hand confirming the site of the lesion.

This was a pretty typical Erb-Duchenne type of case and the only one in our series with indirect type of injury. The other two were both direct injuries and the clinical picture also did not conform to set type.

In one case all the cords accompanying the brachial artery were cut together with the vessel, rendering the elbow joint as also all the structures below it functionless and anaesthetic. The lesion was at the region where the cords break out into their branches. The muscles of the shoulder girdle therefore were spared.

The third brachial plexus case had such severe associated injuries that detailed neurological examination was not done till his general condition improved. He had come with a sucking wound in region of the right apex caused by a bullet which had shattered the clavicle about its middle and had passed through breaking the second rib and the scapula. The injury in this case seemed to be at the level of the trunks and all the trunks apparently were affected as the only movements possible at the end of a week were slight flickers of the pectoralis major and latissimus dorsi. The rhomboids were not tested for, but they must have been intact. The zone of anaesthesia pretty widespread at the outset contracted remarkably at subsequent examinations.

In diagnosing the cases of median ulnar and radial nerve injuries certain simple tests of motion and sensation were relied on. Thus in case of median nerve lesions at the wrist the first test tried was opposition of the tip of the thumb to the tip of the little finger, to reveal the weakness of the adductor of the thumb. Since we did not have a case of lesion at the elbow level, it was not worth while testing the action of the flexors sublimis and profundus, or of the flexor pollicis longus. Abduction of the thumb at right angles to the palm was also tried but found less useful. Thus loss of opposition coupled with anaesthesia in the zone of supply was taken as sufficient evidence of nerve section and later confirmed both the times at operation.

Later on, more marked than the typical deformity, were the trophic changes viz., the tapering of the finger-tips, cold, blue, shiny skin which later turned red and warm (and remained so for quite some time in one of the two cases) and even the change in texture of the nails on the affected finger.

In the ulnar nerve lesions one case came to the hospital with a typical deformity whereas the other had such a big gash on the medial aspect of the elbow that neither left any doubt as to the lesion in the nerve. And as both these cases were neither able to form a cone with the fingers nor grasp a newspaper between thumb and index finger (Froement's Sign) it only remained to test pinprick sensations of the little finger to clinch the diagnosis.

With regard to radial nerve lesions particularly as most of the cases were of "Partial Interruption" only, more reliance was placed on inability to extend the fingers than on inability to extend the wrist. In either case the test was carried out with the hand and forearm.

living prone on the table in order to eliminate the apparent extension caused by strong flexion of the fingers and also to eliminate extension of fingers by interossei and lumbricals

Of the two combined median and ulnar injury cases, the one that came some time after the injury with what seemed to be complete interruption of both nerves, recovered remarkably well after operation and though the complete "ape hand" deformity stayed unimproved the function with particular reference to regeneration of sensation was extremely gratifying. His hand even today looks wasted and red but he is none the worse either for the look of it or for the residual weakness.

The other case a gunshot injury in a Mohamedan woman ended up as an atypical irritation syndrome. She could not be put down as a definite case of causalgia as the pain she occasionally complained of was more in the zone surrounding the wound than lower down in the limb, the trophic changes also were not very marked, but she did not improve with conservative treatment and refused further interference.

Our case of posterior-interosseous nerve injury had other nerve injuries that were equally interesting. A stab wound in the region behind the left parotid gland had severed the eleventh and twelfth cranial nerve giving rise to what is called Jackson's syndrome or Bull-fighters' syndrome, which had resulted in a hemiatrophy of the tongue with difficulty in swallowing, particularly fluids which regurgitated through the nose. The trapezius was weak, but the weakness of the sterno-mastoid was more marked. The posterior interosseous had been severed only in part resulting in loss of extension and abduction of the thumb and index fingers. The lesion evidently being below the branches to extensors digitorum, digiti-minimi and carpi-ulnaris.

Prognosis

The factors governing the prognosis of nerve-injuries particularly as regards regeneration could be laid down as follows

(1) The individual nerve injured

In general it may be said that those nerves with only one type of fibres (viz., motor or sensory) predominating, and those subserving cruder functions, regenerate better than nerves that are predominantly mixed and those that subserve finer or more evolved functions.

Thus a radial nerve predominantly motor is expected to regenerate better than median or ulnar which are more mixed and subserve more intricate movements.

(2) The level at which the injury occurs—

- (a) The longer the distal segment the worse the prognosis,
- (b) The closer (proximally) the section is to bifurcation or branching the worse the prognosis. Thus the prognosis of the posterior interosseous which branches off immediately is bad.

(3) Type of injury, condition of the nerve ends, of the wound and of the nerve bed. Thus gunshot wounds have a bad prognosis because of very definite contusion effects (as seen by the microscope) for a long distance in and both the proximal and the distal ends, which later goes on to necrobiosis and dissolution of the nerve-tissue.

The resulting pattern of regeneration of the nerve is therefore more confused

- (4) The other important factor governing prognosis is the time interval between injury and suture. If this is over two months, irreversible changes occur in the distal segment, as also in the tissues supplied, which hinder regeneration and recovery

- (5) The type of treatment and after care are also important factors

Thus grafting has a definitely bad prognosis, the causes of this being so, will be discussed in the section on treatment. In cases of suture, mechanics of suture

- (6) Lastly, the degree of interruption and the latent-period duration have prognostic significance. The latent period comprises of—

- (a) Initial delay at site of injury before fibres appear at the distal segment

- (b) The time taken by them to advance to muscle or cutaneous ending

- (c) Terminal delay for end-organ regeneration

The most noteworthy thing about our cases of nerve-injuries was the recovery of the median-nerve lesions. Contrary to expectations all three cases in which the nerve had been sutured progressively improved and recovered more than 50 per cent of the function in each case. The change was most remarkable in the recovery of the sensation. We were at first sceptical about the contraction of the area of anaesthesia, considering it to be overlap, but with the passage of time almost complete sensory regeneration occurred in one and a good 60% in the other two. Even the case of the combined ulner and median injury the patient recovered his sensations (to pin-prick at least) completely over the whole hand. The radial nerve cases true to type bore out the good prognosis given and two of the four recovered completely, one did not come for a follow-up and the one that ended up partly as failure was more due to inadequate treatment (*viz.* suturing) fracture as also due to a flail arm (non-Union fracture Humerus). I saw this case about two weeks back. His humerus is soundly united now and he can extend his wrist to a considerable extent but not so the fingers.

The prognosis in both the ulner cases was made worse by the type of injury in one case and the time factor in the other. In the first case the patient had almost half his elbow blown off by a bullet and there was no chance of the wound healing by primary intention, besides the associated bone and joint injury was almost certain to lead to a stiff immobile elbow and repair of the nerve at no stage was even thought of.

The other case came to us with the claw-hand deformity already in existence for over a year, and freeing and transposing the nerve to the front of the elbow did not make any difference in the clinical condition.

Since the two cases of Causalgia were not given full or even adequate treatment the prognosis as to relief and recovery remains in doubt.

Treatment

Sydney-Sunderland has recently published an article in the B. J. S. on his "Observations on the Treatment of Traumatic Injuries to Peri-

pheral Nerves" wherein he discusses the relative merits of conservative and radical treatment of about 350 patients followed up for a period of five years

He mentions that recovery following conservative treatment was (with rare exceptions) complete or unquestionably superior to that which could be expected from surgical repair under the most favourable conditions

In his series of cases there were 68% of spontaneous recoveries. Of the 31% explored 6% required treatment and subsequently recovered spontaneously. He discusses that the policy of exploring injured nerves with complete interruption as soon as local conditions permit is good because

- (1) Early repair is permitted thus shortening the period of incapacity, while irreparable damage is treated without delay
- (2) Chances of a successful nerve-suture diminish after delay beyond two months, due to irreversible changes in the distal segment (Contraction of the lumen of the regenerated neurilemmal tubes) and in the extra-neural tissues (perineural fibrosis)
- (3) In skilled hands exploration is safe. But he warns that if in an exploration, a nerve is found to be in continuity it should not be divided or resected and regardless of apparent damage it should be allowed to recover spontaneously

A delay of six to nine months in such cases does not adversely affect the suture results. If the nerve treated thus does not recover spontaneously then re-exploration with resection is indicated

As regards neuroma, he says that the mere presence of a neuroma is no indication for resection and suture, it is better to allow maximum amount of spontaneous recovery before interfering

The general principles of nerve repair as laid down in the War Manuals of Neuro-Surgery are. If the wound is seen *within six hours* thorough debridement and primary nerve-suture is recommended provided the nerve is not much contused, the surrounding tissues not lacerated and the ends as also the skin margins can be apposed without tension. In cases where sulfonamides have been used locally and systemically this period can be prolonged to almost up to 18-24 hours

If the wound is seen later than this, the infection is to be treated to secure sound healing, and the suture of the nerve is to be carried out at a secondary operation performed at least 3 months after sound healing (unless sulfonamides have been used in which case this waiting period could be curtailed to as many weeks)

All authorities do not agree with the views stated above. Some advise primary suture only in cases seen within three hours of the injury local conditions permitting. Others advocate delayed-primary-suture in all cases (to be done within 3 weeks of the injury) stating that this is the optimum time, as the nerve-sheath in both segments and the axons in the proximal segment has regenerated sufficient within this period to give effect to maximum regeneration if the nerve is repaired at this stage. They also mention the disadvantages of earlier and later suture, pointing out the sepsis, and devitalised state of the tissues in the former and the irreversible changes in the

distal segment in the latter which hinder the progress of the regenerating axons

The views regarding the use of sulfonamides locally are also varying, as according to some the irritant effect of these on the tissue leads to more fibrosis which is very definitely detrimental to the cause of regeneration in a sutured nerve. Loyal Davis does not seem to hold this view as he clearly states that sulfonamides have no deleterious effects upon the healing and regeneration of sutured nerve.

Regarding the use of suture material mention should be made of "Fibrin Suture" wherein the apposed cut ends are resealed together by a "Glue" of concentrated plasma coagulated by chicken embryo tissue-extract. The ends are held together in a special cup prepared for the purpose. This type of suture is supposed to give rise to the least amount of fibrotic reaction and therefore yields the best results.

The maintenance of the limb in adequate position and mobility as also the proper state of nutrition from the time of injury to that of final recovery is of prime importance.

This is particularly necessary, where due to unfavourable conditions immediate repair of the nerve has not been possible or where due to the type of trauma, later treatment particularly grafting has been necessary.

Our attitude as regards treatment of our nerve-injury cases was more or less as mentioned in text-books viz

"Radical in nerve exploration and Conservative in nerve operation"

As a matter of fact we were a little conservative regarding our explorations also. Thus in the brachial plexus injuries, no exploration was undertaken to ascertain the exact amount of damage. The rationale employed for not exploring early was to allow the establishment of collateral circulation, as in two of the three cases there was no radial pulse at the wrist and in one of these, from the history it was ascertained that the artery had been severed. As for the third case, the very nature of the injury did not warrant an exploration.

Regarding the other cases (viz two cases radial nerve injury) radical exploration was not undertaken while debriding the wound mostly because the operating surgeon (viz the house-surgeon) did not consider himself competent enough for the task, and as subsequent progress in these cases led to almost complete recovery, the conservative attitude seemed justified.

Whenever during debridement however, the cut nerve ends presented themselves in the wound, as they did on six occasions, the wound was further explored, the nerve ends mobilised and as on five of these occasions the local conditions were found to be favourable, an end to end suture was undertaken and carried out.

Of the nerves thus sutured primarily were two median at the wrist and one in the fore-arm. One radial at the wrist. One sciatic in the thigh (middle).

The case where in spite of visualising the nerve in the wound nothing constructive was done, was where the ulner nerve was seen torn and the ends severely contused, with the humerus broken to bits in the neighbourhood.

The results of these primary suture cases will be discussed later.

Delayed primary suture was never done in any of our cases.

Secondary suture was done in two of our cases and the total number of nerves thus sutured were five. Thus in the case of combined median and ulnar injury both these nerves were sutured one after excising an attenuated band connecting the ends and the other after a neuroma resection. The other case was that of a brachial-plexus-cords injury with severance of the brachial artery. All three cords had to be sutured.

Neurolysis was carried out on four occasions two of these being the causalgia cases, one median and the other sciatic, the former was freed right upto the wrist from the elbow and placed in a new bed between the muscle and the subcutis. In the latter case the affected segment was freed from fibrous tissue and placed in a cover of fascia-lata before reposing it to its bed. The third case of neurolysis was that of a lateral popliteal involved in the scar of bomb-shell wound. The weakness of the muscles in this case improved visibly after liberation of the nerve.

The last case of neurolysis was that of a brachial plexus injury.

Apart from these an ulnar transposition was about the only other operative procedure carried out in our series. In one case where the radial nerve had been accidentally severed during bone grafting operation the ends were apposed by a few sutures. This case has recovered considerable power of wrist extension by now.

In the remaining cases conservative treatment was carried out in the form of immobilisation of the part, prevention of contractures in and elongation of the affected muscles and tendons by adequate splintage, prevention of stiffness of joints by passive and active movements, and maintenance of the nutrition of the structures by physiotherapy in the form of massage, radiant heat, contrast baths, etc.

Table IV summarises the treatment given.

TABLE IV

	Conservative	Neurolysis	Primary Suture	Second Suture	Transplantation
Brachial plexus	1	1		1	
Median and Ulnar	1			1	
Median		1	2		
Ulnar	1				1
Radial	2		2		
Posterior Interosseous	1				
Sciatic		1	1		
Lateral popliteal		1			
Femoral			1		

Follow up and Results

The follow-up of our cases was to say the least poor. Although every effort was made to contact the cases after discharge, to induce them to attend at regular intervals for a check-up of the progress and assessment of the residual defect. The number of patients that cared to reply to our reply-paid post-cards was less than half. Fortunately one or two patients had been kept in the infirmary for secondary operations and one or two turned up for other complaints thus enabling a follow-up till almost a year, of about 55% of our cases. Due to the panto-stat machine being out of order now and then, the check-up on electrical reaction could not be carried out on all the cases. Thus

ten out of the nineteen cases were reviewed after discharge, four of these more than once

The results as gauged from this crude follow-up were very satisfactory particularly in the light of the treatment given, thus confirming the view of Mr Sunderland that it is best to leave an injured nerve alone and allow it to regenerate naturally to the maximum extent, before interfering

Thus of the six cases where the nerve-injury was treated conservatively the two radial nerve cases recovered completely, the case of median and ulnar had a residual neuritis, but the functions sensory and motor were almost as good as on the normal side. The brachial-plexus case was improving gradually but has not turned-up for follow-up after discharge (probably because he has recovered completely). In the ulnar nerve case the nerve was smashed beyond repair so nothing could be done. The last case viz the post-interosseous nerve, is a doubtful case, one wonders whether he would have done better with a suture, this operation was not carried out during his stay here partly because of bad prognosis but mainly because he was not keen on any operation till he had claimed his compensation. This gives us a good 65% of cases recovering over 75% of the function

Results that could compare with any other form of treatment

Of the four cases in which neurolysis was done, only one seemed to have derived real benefit, this was the case of the sailor whose lateral popliteal had been involved in a sharpnel scar. The recovery of power in the dorsi-flexors of the foot was very satisfactory, though the sensations did not recover to the same extent. Due to lack of follow-up it could not be determined whether the sensations did improve later or not. The two causalgia cases derived very little benefit indeed, and the same can be said about the brachial plexus case

Of the seven cases on whom primary suture was carried out, three definitely failed one of these being due to faulty technique, one could not be followed-up and three regenerated to varying degrees, strangely enough all these three were median-nerve injuries. Of these, two cases where the nerve was cut at the wrist responded very well, in one the sensory recovery is absolutely complete though evidence of trophic disturbance still remains. The other one attended the Outdoor till the sensations had crept up to the distal phalanges and has not shown up since. In the third one the sensory regeneration was proceeding quite satisfactorily but the patient has not come for subsequent check-up. Of the two radial cases one has never returned after discharge and the other failed partly as the ends were only brought together by a few sutures and not formally sutured. The sciatic at no stage gave any hope of recovery. As for the femoral, the muscle power gradually improved a little but that probably was due to the quadriceps drill and not due to nerve-regeneration

Of the three cases in which secondary suture was performed only one viz, the median and ulnar case improved visibly. He has now excellent function in the hand and can make out light pin-touch all over the hand and fingers

Of the brachial plexus cases one has not been followed-up long enough and the other one after slight improvement has remained "status quo"

The ulnar transposition did not improve
Table V summarises the results

TABLE V

	No Recovery	Spontane- ous recovery	Foll pri suture	foll 2nd suture	Foll neurolysis
Brachial plexus	1	1			
Median and Ulnar		1		1	
Median	1		3		
Ulnar	2				
Radial	1	2	1 not traced		
Post Inteross	1				
Sciatic	2				
Lat Popliteal					1
Femoral	1				

SUMMARY

1 Nineteen cases of peripheral nerve injuries have been reviewed with almost one year's follow-up in about half the number

2 The results of conservative treatment have been found to be superior to these of active interference 65 per cent of these cases spontaneously recovered more than 75% of function

3 The results of primary nerve suture of the median nerve have been found to be very gratifying All three cases showing progressive improvement upto their last visit one having almost completely recovered function

4 A fairly severe case of causalgia treated only by neurolysis (no interference to the sympathetic chain) seemed to get adapted to the condition with the passage of time and leads a fairly useful life

I take this opportunity to express my gratitude to my chief Dr R J Katrak, F R C S (Eng), for his kind help and guidance in preparing this thesis

I also thank Dr R G Glade M S (Bom) for his guidance in preparing the scheme

I am also obliged to Dr R G Dhayagude, M D (Bom), the Dean of the K E M Hospital for allowing me to go through the case reports of the hospital

Clinical Case Reports

DEREALIZATION—DEPERSONALIZATION SYNDROME—

N D PATEL, M D

J G, a married brahmin of 45 years, seen on 28th October 1948 had not left his room since 31st January 1948, the day on which his car had got involved in some political demonstration and was stoned. He was not hurt physically in any way. He came home in a fright, took to bed and said that (1) there was no blood in his veins and arteries, (2) his head was empty, without any brain tissue, (3) he had no strength in his muscles, (4) he had no nerves, and (5) he could remember nothing.

No argument or persuasion could convince him of the unreality of his beliefs. He would not leave his bed or room. He made his son give up college studies and put him in charge of his business. He was seen by several physicians and treated with sedatives and suggestions, without any effect. During this period he got much depressed and sometimes talked of suicide.

On examination on 28th October 1948, he was co-operative and sensible, a little puzzled and depressed. He complained of absence of any blood in his veins, any brain in the skull, any strength in the muscles or nerves, and forgetfulness. He was apathetic but could talk freely about his past, his business, or on any subject quite rationally. There was no evidence of retardation.

The physical examination did not show any evidence of organic disease. The past history was negative except for an attack of pneumonia in 1937. The family history was non-contributory. There was no history of addiction to *Bhang*. The patient was a self-made man, had come to Bombay in childhood, worked as a hawker, fruit-stall keeper etc., and had risen up in business, acquiring much property and establishing a sound perfumery business. He was happily married for 23 years and had three grown up children.

Because of depression and ideas of suicide electric convulsive therapy was advised. The patient willingly agreed to come for treatment to a nursing home but next day disappeared from the house and after some ten hours' search was found walking about on the sea-shore. He was persuaded to go home and was brought to a nursing home for treatment the next day.

In the nursing home he was given a course of electro-shocks. During the early part of this treatment he persisted in his feelings of unreality, such as he had no blood, no brain, no strength, etc. When blood was removed from his vein and shown to him he merely laughed and said "But it is not blue blood!" He would not get up and walk. He persisted in saying that his head was empty, everything, all about him, was empty. He would become suspicious if you disbelieved him, laugh or smile knowingly, and withdraw within himself. After four electric shocks he showed remarkable improvement, now he would get up and walk, go to bath room, and laughed if told about his lack of blood or strength. Still he maintained that there was no brain, that his head was empty, and that he could not think or remember things. He talked very rationally with his relatives and made detailed enquiries about his business. After four more shocks assisted by reassurance and explanation of the mechanism of anxiety, his feelings

of unreality and depression disappeared and he left the nursing home in a state of remission

Derealization—Depersonalization Syndrome has been recently described as a clinical entity. Its chief features are a subjective feeling of changed personality and altered reality, the patient feeling that the outside world is changed and has become unreal, and a feeling that patients' own body has altered and become unreal. To this feeling of unreality and depersonalization are added (1) a marked degree of apathy, depression, even leading to suicidal attempts, and (2) a distressing sensation in the head—"my head is heavy, not working properly, is empty, is numb, cannot think clearly, cannot remember, etc."

There is no alteration in consciousness, rapport or insight. Other thoughts are quite rational. There are no hallucinations, delusions, retardation, conduct-disorder, or mental deterioration.

Physiologically, such a state of mind is produced by administration of small doses of mescaline. The syndrome is refractory to psychotherapy, sedatives, and euphorants (such as benzedrine) drugs. In fact the last group of drugs is likely to worsen the condition. Clinically, the syndrome is very likely a form of Depression and has to be differentiated from psychoneurosis or hysteria. Therapeutically, electro-shock therapy gives the best chances of early remission.

Critical Notes and Abstracts

THE PRACTICAL IMPORTANCE OF MODERN CONCEPTS OF PSYCHOSOMATIC RELATIONS (Alfred O Ludwig, M D Boston, New England Journal of Medicine, February 5, 1948, 238, 175-178)

The term psychosomatic in its present-day usage serves commonly to designate a group of diseases with organic changes in which emotion is thought to play an important etiologic role

The recent investigations in this field are an approach toward incorporating into the structure of medical science what used to be known as the art of medicine. Every one is familiar with the consummate skill of the experienced general practitioner, which combined a detailed personal knowledge of the patient, his past life and his family with sound medical understanding as well as a great intuitive grasp of emotional problems and a warm friendly support. Striking therapeutic success and an excellent doctor-patient relation were often the result. However, these efforts could never be more than intuitive or empirical, nor could they be made predictable or manageable until they were subjected to careful psychiatric investigation.

To consider the patient as a person one must first accept the reality of emotional reactions. For example, one should not forget that nausea and vomiting may be caused entirely by strong emotions as well as by structural changes or by irritating substances in the stomach. Somewhat more difficult to visualize but now well established is the concept that emotion can eventually produce structural changes in the body. Once this is admitted a far broader view of the nature of disease must follow.

One must make certain that the patient's feelings, his personal relationships, his life situation and his reaction to his environment are all subjected to the same painstaking scrutiny as his physical body and its symptoms. His emotions should be examined with the same objectivity as his organs, and here it is well to caution that moral judgment regarding behavior has no place in medical treatment. Irritating or annoying actions can be as much a part of a pathologic picture as organic disease and should receive from the doctor the same dispassionate appraisal, never unreasoning retaliation.

The first group of disorders of importance to the practicing physician are neuroses that manifest themselves by somatic disturbances, such as gastro-intestinal, cardio-vascular and skeletal symptoms.

It is highly important that such patients be handled properly from the outset. This implies that one take a careful medical history, which should include at least an attempt to outline the gross personality traits as they pertain to the illness. An adequate physical examination should follow, with special attention to the part of the body that is the seat of the complaint. Necessary laboratory work should be done when indicated.

At this point the physician can make or break the successful treatment of the case. If no significant organic changes are demonstrated, the patient should be so informed and should then be instructed, in the simplest words, concerning the mechanism of production of psychogenic symptoms. All explanations should be clear and concise,

and the patient should be encouraged to ask questions to allay any fears that he may have

If the disease is purely psychogenic, treatment should not be organic. Every neurotic person seeks to evade responsibility by falling back upon an organic diagnosis. It is more comfortable and more acceptable to explain symptoms as due to alien infections or other external causes than to accept personal responsibility as one must if one's own emotions, be they conscious or unconscious, are at fault.

Unnecessary surgical procedures are especially harmful. In the presence of severe neurosis, the patient may often unconsciously seek such treatment in part as punishment for severe guilt feelings.

Another important category of illness is made up of disorders in which recent studies have shown that emotional influences acting over longer or shorter periods result at first in disturbed physiology and eventually in structural change. Peptic ulcer is the simplest example. Ulcerative colitis is another serious disorder in which emotional factors play an important role. Other disturbances in this group are the allergic illnesses such as asthma, hay fever and urticaria, certain skin diseases, such as eczema, and neurodermatitis, migraine, possibly certain cases of epilepsy, hypertension and rheumatoid arthritis.

Addiction to alcohol and to drugs has long been considered a purely psychiatric disorder. Another addiction—namely, that to food, which leads to simple exogenous obesity and which may result in the complications that are secondary to pathologic accumulations of fat, has been shown to have important psychologic aspects.

There seems to be emerging slowly a clearer understanding of the personality structure of persons who become ill in this way or who react with their bodies to certain emotional crises. These patients, usually unknown to themselves or others, appear to have remained or to have been pushed back to extraordinarily primitive and early stages of emotional behaviour. They manifest an extreme degree of dependence upon certain key figures around them. This dependence on closer survey turns out to be so exaggerated that it suggests an almost symbiotic relationship. The loss of these key persons by death or by separation produces catastrophic helplessness and is often followed by organic illness.

This extreme degree of insecurity and need for the support of others is manifested in various ways. It may be displayed openly as a childish, clinging, extremely demanding and grasping attitude with marked impatience and intolerance to any discomfort. On the other hand it may be completely hidden. In this event only the defense against the underlying weakness is seen in the form of an exaggerated false front of self-reliance and independence. The inadequacy of this defense becomes apparent when it collapses before any event that forces the patient into a dependent attitude. Apparently, many of these persons are extraordinarily dependent on the constant presence of outside help for the maintenance of security and psychologic integrity.

Coupled with this extreme degree of dependence is an exaggerated intensity of emotion. In consequence, these patients become extremely controlled outwardly and are usually considered to be cold and unfeeling.

They fear any loss of control because it may result in an explosive and overwhelming outburst

Contact is difficult and they tend to live in isolation. Personal relations are difficult except on a superficial level. Their greatest fear is that of complete helplessness. Organic illness brings some recompense in that it is accompanied by the security secondary to attention and medical care. However, so great is the fear of relying on others, that patient may resent treatment.

Eating is one primitive method of solving difficulties employed by these patients. For them, eating can assuage a sense of loss, of depression or of deprivation, and on the other hand it may serve to relieve anger or rage. Oral drug addiction is not rare.

These patients appear to have extremely loosely organized personalities. Responses are primitive and of total intensity. In this primitive stage such strong emotions are expressed by physiologic changes rather than by the more mature methods of physical activity, the outward expression of feeling or by verbalization.

What are the implications for treatment? To influence such patients, it is essential to establish contact with them. This requires a very warm, friendly and giving type of approach, such as is usual and customary for the practitioner of medicine.

It will be clear that such vulnerable persons will be suspicious and distrustful, and therefore it is vital that an attitude of extreme honesty be maintained at all times. If mistakes are made, they must be freely acknowledged. Strong support and reassurance are essential, and it is often necessary to infuse one's own optimism, confidence and strength of will into the patient. This he accepts by identification. The doctor may have to put himself temporarily into the role of the lost key figures or seek to manipulate the environment so that they are replaced.

One must never try to push these patients too hard or too fast. Pressure is felt as rejection and hostility and either is strongly resented or produces exacerbation. One must avoid becoming annoyed by demanding and grasping attitudes. Often, these persons deliberately try one's patience by overt hostility. It is best to inquire into the reasons for such behavior, before retaliating. Many of them suspect that the entire world is hostile and cannot believe that anyone has any good intentions. The best results are obtained by gentle suggestion.

Vocational guidance, with retraining when indicated by the limitations of illness, deserves a larger place in organized medicine.

A word regarding the role of compensation and pension in disease is indicated. The justice and humanity of the principle of compensation for injury or illness sustained in industry or war are freely conceded, but a much greater understanding of the insidious and highly crippling effects of a continuing pension must become more wide-spread among the medical profession. Everyone has seen patients pushed into and maintained in chronic invalidism through the payment of weekly or monthly pensions. Such behavior is neither conscious nor deliberate but represents a secondary neurotic dependence that is nurtured by the continued pension. From the point of view of rehabilitation, continuing compensation is not humane but hampers recovery. A review of present attitude toward these practices is necessary.

ON THE PERSISTENCY OF SENSITIVITY TO TUBERCULIN (Wallgren, Arvid *Rev chilena de pediat*, 18 901, 1947)

According to a general concept, sensitivity to tuberculin which appears with the primary manifestation can be eliminated with biological cure of the primary complex, Wallgren emphasizes that the problem of the persistency of sensitivity to tuberculin is not only an academic one but also one of scientific interest, and that its practical significance should not be discounted

It has been considered that sensitivity to tuberculin and specific immunity to tuberculosis have a parallel course to a certain degree, in the sense that they appear at the same time and disappear together. If there is sensitivity to tuberculin after a primary infection, it is considered that immunity does not exist. In practice, this concept of the relationship between tuberculin sensitivity and immunity to tuberculosis, as it happens in vaccination with B C G has been confirmed

If sensitivity to tuberculin has not appeared or if it has disappeared after several years, vaccination does not offer effective protection against a virulent infection, but the opposite happens when the reaction is positive and persists in being positive

Occasionally, children who have not been vaccinated with B C G and who have previously been considered tuberculin positive get ill and show a clinical and radiological picture of a typical primary infection, therefore, they should have been tuberculin-negative before that time

In countries where bovine tuberculosis has been combated in an effective manner, the primary infection is localized with few exceptions, in the lungs. In the natural evolution of the primary complex, the caseous, necrotic parts of the pulmonary lesion and of the hilar ganglia begin to calcify after one or two years, for which reason it is easy to detect them in the X-ray plates. These calcifications are produced to a greater extent in the younger child who survives an infection

A pulmonary calcification with negative tuberculin reaction does not signify that the ability to react has been exhausted in a person with a cured tubercular lesion. In a great number of cases the calcifications may be a result of coccidiosis or histoplasmosis

To be able to affirm that the reaction to tuberculin has been exhausted in these cases with calcifications, it is necessary to show that the children have undoubtedly reacted previously to tuberculin and that at some time B tuberculosis has been evident

Book Reviews and Notices

MEDICAL ANNUAL 1948, Editors Sir Henry Tidy M.D. F.R.C.P. and A. Rendle Short, M.D., F.R.C.S. John Wigh and Sons Ltd., Bristol 1948, Pp 414 Price Rs 16/-

The sixty-sixth volume of this very well-known annual maintains the high standard established by the editors and the publishers. In these days of rapid progress it becomes an extremely difficult task for medical practitioners to keep abreast the rapid changes in the different branches of medicine and critical abstracts and reviews contained in this volume provide essential information in a concise form at a minimum expenditure of time. Each subject is contributed by individuals who are well experienced in their particular specialities and the lexicographic arrangement of the contributions makes the task of reference easy and time saving. The exhaustive references to the original publications serve a very useful purpose for those who are more interested in the details. In spite of the vast expanse of material covered by the book it retains its comprehensive character and brings "the treatment and practitioner's index" upto date.

M D M.

JOURNAL OF THE GUJARAT RESEARCH SOCIETY, Vol 10 No 3, July 1948

This entire number of the Gujarat Research Society is devoted to medical and health subjects and contains much interesting and thought-provoking material. Dr Jivraj Mehta, the veteran medical administrator, reviews the medical and health problems of Maha-Gujarat, which may well apply even to the whole sub-continent of India, and envisages a medical utopia, which gives a fair promise of being a panacea for the ills of the people as well as the medical men. The only difficulty seems to be the prospect of its achievement in any reasonably near future. Dr Pathak has taken up the work of statistician to the society and surveyed the work of the two health centres run by the society. This idea of positive health is very welcome at this moment of medical reforms in our country but the response to this effort does not seem to be satisfactory, judging from the work put in by these centres. Dr Jhatakia and his colleagues have made an attempt to review the causes and characteristics of anaemia in a Gujarati Hindu population of a city hospital and come to the conclusion that the main aetiological factor is nutritional deficiency, resulting from an inadequate diet. Dr Pathak analysing the food of medical students, for a short period of ten days, comes to an almost similar conclusion regarding the nutritional value of their diet. In a well presented paper Dr Chamanlal Mehta makes a scathing attack on the failures of the Bombay Government to keep up with the promises made by them regarding rural medical relief as early as 1946. In a fearless manner he points out the defects and shortcomings of the various unscientific and impracticable schemes launched by the Government and makes a plea to the Health Ministry to utilise the valuable cooperation offered by the independent medical profession and not to fight shy of it like the former alien government. This is a sound piece of advice which deserves the attention not only of our provincial government but also of other governments who have the good of their people at heart.

M D M

RECENT ADVANCES IN THERAPEUTICS, J. R. Goyal, M.B.B.S., 3rd Edition, 1948 Pp 288, Price Rs 7-8-0

The 3rd edition of this book is published after a lapse of four years. Therapeutics is perhaps the main interest of the general practitioner

and it is not possible for a majority of them to be conversant with all or even many of the rapidly changing ideas in therapeutics. To such as these Dr Goyal's book is a great help in keeping up with the times. In his enthusiasm to make the book as complete as possible Dr Goyal has included some therapeutic measures which are still in the experimental stage and are not definitely meant to be used in practice without strict controls and a thorough appreciation of their shortcomings and dangers. The sections dealing with the sulpha drugs and the antibiotics are particularly exhaustive and will help a good deal in the rational use of these drugs. Without entering into pedantic discussions, which are obviously beyond the scope of this manual, the author has succeeded fairly well in making a concise resumé of the recent advances in therapeutics.

M D M

ILLUSTRATIVE ELECTROCARDIOGRAPHY Julius Burnstein, A.B. M.D. and Nathan Bloom M.D. F.R.C.P., 3rd Edition, D Appleton Century Co Ltd New York and London, 1948 Pp 309

With an all round increase in the incidence of cardio-vascular diseases and particularly of "coronary disease," it becomes more and more imperative that every medical man should have some basic fundamental ideas about the rapidly progressive branch of electrocardiography. This at last by Drs Burnstein and Bloom fulfils this necessity to a very great degree. The book deals with the practical aspects of interpretations of the E.C.G. without confusing the issue with the theoretical discussions of the physics, mechanics and the electrodynamics of the heart and the electrocardiograph. The book is essentially meant for the clinician and makes no pretensions of helping the research worker in the complicated subject of electrocardiography. The graphs are well marked and the legends are clear and concise explaining why the particular conclusions are reached. The grouping of the subjects is of a type that gradually leads the student from the simpler to the more advanced type of tracings and easily builds up the confidence of the student in the interpretations of the complicated records. The inclusion of the precordial leads and the unipolar leads elevates the book from the class of a mere primer of electrocardiography to that of a book for the beginner as well as for the advanced student. Obviously the unipolar leads do not occupy many pages as the theory and complicated discussions are purposely avoided. The inclusion of a chapter on the Radiology of the heart is an addition in the right direction and serves to explain the various changes that may be brought about in the tracings obtained from a heart which is functionally normal but shows a different pattern by virtue of a change in position or its electrical or mechanical axis. We can confidently recommend this book to those who have a desire to be initiated to electrocardiography and as a first step for those who aim to be specialists in this interesting and useful branch of medicine.

M D M

MEDICAL FEES

Honour a Physician with the honour due to him

(BEN SERA—*Book of Wisdom*, c 190 B C)

There is no uniformity of fees charged by medical men in different cities of India and perhaps there cannot be, because of different economic conditions. The Calcutta physicians charge Rs 8, 16, 32 and 64, and even 128 for consultations or visits. In Bombay, the most prosperous and premier city of India, the consultation and visiting fees of the consultants have long been Rs 10 and Rs 20 and the most amazing practice is that the general practitioners do not charge their patients for medical examination and opinion! Recently some consultants have raised their consultation fees to Rs 15, 20, and 30 and visiting fees to Rs 30, 40, and 60. It is reasonable that there should be some kind of uniformity and gradation of fees according to the physician's experience and standing. *It is not possible to measure a physician's services to his patients in terms of cash.* Our colleagues, the Barristers, call the fees they charge as *Honorarium*. Similarly the fees paid by the patients to the physicians is really an honorarium and not a measurable equivalent of the services rendered. If a surgeon charges a huge amount for an emergency operation nobody can deny a physician a similar right when he sees a patient through a serious attack of pneumonia, or typhoid, or meningitis, or myocardial infarction, where his judgement and skill in diagnosis and treatment may be exercised to meet several emergencies. In some countries the surgeons make their bills after consulting the income of their clients and there is no reason why practitioners in India should not do so. There is no law, custom, or usage to prevent them from doing so.

It is time the general practitioners in Bombay charged their patients for examination and opinion, say, anything from Re 1 to Rs 10 and visiting fees from Rs 2 to Rs 20 according to their professional standing and experience, and the economic status of the patient. The consultants too should have three or four grades of fees according to their professional training or standing. For the first 10 years of consulting practice, one may suggest, the consultation and visiting fees may be Rs 10 and Rs 20, for the next 10 years Rs 15 and Rs 30, and for the next 10 years Rs 20 and Rs 40. For those who continue a *limited practice after retirement* the fees may be Rs 30 and Rs 60 or even more.

The medical man is asked to do free service, here, there and everywhere, because he gets experience in practice! The way in which this need for experience is exploited by the State, the Municipalities or Local Boards, and Charitable institutions is really preposterous. Medical man's work is humanitarian. He has to deal with ill persons, whose earning capacity is affected for the time-being and whose expenses have gone up because of illness. All this is readily granted by us. But one must not forget that the medical man also lives in an acquisitive society. He has to maintain his standard of living, look after his family, educate his children, and provide for his old age. To appeal to his humanitarian sentiment and to leave him to starve ill becomes a state or society. It is also true that private modern medical treatment is very expensive at present and perhaps beyond the reach of the poor.

and even the middle class. The remedy for this state of affairs is a comprehensive state medical service and free medical education. Till this comes medical men must charge their patients according to their social and economic status, and the state and society must pay adequately all their medical employees. No other young graduate, teacher, lawyer, or engineer, is exploited in the way a medical graduate is exploited to-day. No man or institution values one more than one values oneself. It is a common experience of physicians that free advice given to patients is rarely valued highly, the patient often rushing to get a second opinion, and the honorary services rendered to the state or to the municipality are also valued little and taken as a matter of course.

"Where there is no fee there's no skill"

—ARISTOPHANES

"The doctor who accepts no fee is worth none"

—BABIL TALMUD

Reflections and Aphorisms

1 "An *imaginary pain* is a contradiction in terms If I say I have a pain, I either have it or I am a liar There is no possibility of my having a pain which is not present" (T A ROSS)

2 "A man *believes* that his neighbour is using some electric apparatus which results in giving him severe pain in the head His belief in this is of the same order and fixity as mine is that I am now sitting on a chair If anyone tried to prove to me that I was not sitting on a chair I should not listen, if he persisted in his arguments, I might in time get angry In exactly the same way, with same force and intensity, the man who believes in fantasy believes in the reality of the hostile electric apparatus He will not listen to the arguments of anyone who tries to convince him of the unreality of his belief, and soon any argument about it will make him angry" (T A ROSS)

3 "The patient says that she *cannot*, the nurse says she *will not*, the truth is that *she cannot will*" (SIR JAMES PAGET)

4 "A cure is not of itself a criterion of much value in determining the validity of a theory One must always allow for the effect of *faith*, and *hope* When belief is present in abundance the theory works, when it begins to fail the theory begins to fail too That is why the believing, zealous enthusiast gets the most cures, the critical, unconvinced some cures, and the doubting disbeliever the least number of therapeutic successes" (T A ROSS)

5 "When hope is predominant all the glands of the body perform their functions in a satisfactory manner when the opposite condition is prominent the reverse happens The *daily dose of hope* which a good and careful doctor inspires is no mean factor among those influences which will turn the scale in favour of recovery 'Always do something,' said a wise physician, 'always do something at each visit in a chronic case, even if it be only to rearrange the pillows'" (T A ROSS)

6 "It is part of the cure to *wish* to be cured" (SENECA, *Hippolytus*)

7 "Our remedies oft in ourselves do lie,
Which we ascribe to Heaven" (SHAKESPEARE, *All's Well That Ends Well*)

The Indian Physician

VOL VIII NO 3

MARCH 1949

WHOLE NO 87

Original Contributions

HYPOSPADIUS

by

DR R H KARMARKAR, F R C S (Eng)

My object in reading this paper on hypospadias to-day is to place before you the more recent advances in this field of surgery and to narrate to you my experience of treating five cases of hypospadias. I have reviewed all available literature on this subject from that of 1941 onwards. There is a variety of operations devised to cure this congenital anomaly. Their great number indicates that no single operation is yet found to give uniformly good result. It is well recognised that the end results of these operations, even in the best of urological clinics are often disappointing. However a review of the recent methods shows that sound principles are evolving out of a chaotic state and more attention is being focussed on these principles rather than on elaborate procedure.

Historical—The first efforts towards the surgical treatment of congenital defects of the urethra were those of Dieffenbach in Germany. His paper was translated into English and published in the Dublin Medical Journal by John Swift in 1836. Later Thiersch devised his operation for epispadias in 1869 and in 1874. Auger treated a case of hypospadias using Thiersch's technique. From 1874 to 1886 Duplay published three papers describing his method. Duplay's technique is wellknown to the present generation of surgeons. At the turn of the century one more contribution appeared and that was by Bucknall in 1901. This was followed by that of Ombredanne in France in 1911 and Edmund's Hunterian Oration in 1926. In the common textbooks the methods of Duplay, Edmund and Bucknall, are mentioned and well illustrated but Ombredanne's operation is not to be found in any one of them. Two or three American urologists have recently drawn the attention of the surgeons to the utility of that operation as will be shown presently in the latter part of this paper.

The less known contributions come from Russel who described an operation for severe hypospadias in 1900 and Blair who wrote about scrotal hypospadias in 1933. Van Hook and Mayo described their tunnelling operation in 1901 and Beck and Burghard their operations for glandular types of Hypospadias.

In short all the operations devised and adapted upto 1937 fall into the following two categories —

A paper read before the 85th meeting of the Seth G. S. Medical College and K. E. M. Hospital Staff Society on 11th September 1948 with Dr R. N. Cooper in the chair.

- (1) Flaps taken from the penis, prepuce, scrotum or abdomen or a combination of these and utilised in the techniques of Duplay, Beck, Bevan, Cecil, and Ombredanne
- (2) Free grafts used for being placed in a tunnel made in the glans and shaft of the penis in the procedures of Van Hook and Mayo, Esser and Nove-Josser and transplants from the ureter, vein and appendix.

Of these the techniques where flaps are used have come to stay as acceptable methods

Classification—Three degrees of deformities are recognised viz, the glandular, the penile and the perineal. In the penile variety which is most commonly met with, the meatus may be situated anywhere between the glans and the penoscrotal junction, while in perineal variety other anomalies such as undescended testis, bifid scrotum and pseudohermaphroditism are present

General Rules—I will now discuss certain principles which can be laid down as general principles to be followed in doing this branch of plastic surgery, viz, (1) Suitable age of the patient, (2) Proper handling of the tissues, (3) Choice of suture material, (4) Haemostasis, (5) Asepsis, (6) Psychology of the patient and (7) Attitude of the patient or his guardian to the total duration of treatment

1 *Age*—Consensus of opinion appears to favour the view that straightening of the penis should be done fairly early in life, though not before the age of four. Reconstruction of the urethra has been taken up by various surgeons at varying ages before puberty and at any age whenever the case presented itself for the first time after puberty. The ideal age is between the age of 11 and 16, "before the child becomes embarrassed by the defect." This age group is to be preferred to the younger age group because the tissues are more firm and easy to handle and better vascularised than in infancy. Sutures are more easily applied on a larger phallus than on one of smaller size. In spite of these advantages cases have been operated upon successfully at a much younger age by Goldstein following Ombredanne's method, one case being 2½ years, and another 4 years. Young and Benjamin of Rochester advocate operation at a very early age, one of their cases having been done in one stage at the age of 18 months.

2 *Tissues*—Many surgeons have come to grief because in spite of elaborately planned operations success is not to be had only because the handling of the tissues is rough. As a result they become macerated, dry, torn or buttonholed. The length of time spent over the operation also counts a great deal. As Goodhope puts it "Wound healing in all plastic surgery usually varies inversely with the time consumed in doing a procedure and directly with the gentleness used in the handling of the tissues."

3 *Sutures*—Suture material should be such as would exert a minimum tissue reaction. The following are in common use

- (a) 0000 to 000000 plain or chromic catgut for the urethral tube
- (b) Deknatel C Black silk 000000, for the tube as well as the outer skin
- (c) Malleable silver wire
- (d) Stainless steel wire

Catgut however thin it may be does give rise to some oedema and therefore chances of the sutures cutting through are inherent in its use. Dacknattel or any other silk or linen or cotton of similar thickness seems to be the material of choice for many reasons. Lowsley and Kirwin describe their operation being carried out with buried silver wire stitches and in spite of fistulae formation following its use in their case they advocate its utility. Goodhope has described a technique of using stainless steel wire. A special $4\frac{1}{2}$ inch atraumatic needle with a swedged in 8" stainless steel No. 30 wire suture has been made for him by Davis and Geck. After adequate mobility of the tissues has been obtained their edges are brought in contact with each other and threaded on the needle. If the suture line is satisfactory the wire is drawn through the tissues and fixed in place by placing lead pellets over their ends. The wire is pulled out when the union is satisfactory, at the end of 12 to 14 days.

4 *Haemostasis* has to be perfect even at the risk of putting too many ligatures. Charnock and Kiskadden (1948) advocate a technique of infiltration of the subcutaneous tissues with a local anaesthetic solution (1% procaine mixed with adrenalin solution 10 to 20 drops per 1 oz.) before raising flaps from the penis to ensure perfect haemostasis.

5 *Asepsis*—Asepsis is maintained throughout the plastic procedure. Sulphonamides and penicillin have been of great use in maintaining the asepsis postoperatively. One factor which introduces sepsis and thus spoils the result of a good operation is the passage of urine over the suture line. This is discussed a little later in this paper.

6 *Nursing*—The nurse plays a great role in the ultimate success of this operation. At the Johns Hopkins Hospital the nurses (Lucille Wright & Prince¹²) are specially taught that when the suprapubic or perineal urethrostomy is done it is their duty to see that the indwelling catheter is flushed daily with a sterile lotion and kept free from blockage due to deposit of phosphates in the bladder. Otherwise it is quite common to get the bladder distended in spite of the catheter and the chances of the urine leaking through the normal urethra are enhanced. This is bound to vitiate the result and end in fistulae. The operative area therefore must be kept dry. The nurse should note immediately any stoppage in the drainage and report to the surgeon. Secondly, postoperative cleanliness of the wound, keeping it dry and lightly dusted with sulphonamide powder helps in the prevention of stitch abscesses and consequent fistulae. Thirdly, at the Johns Hopkins Hospital the nurse is instructed to apply an ice bag with very little ice in it and for as short time as is necessary whenever the patient feels that there is danger of an erection of the penis. Higgins¹⁶ (1947) believes that the first erection causes the sutures to be pulled out and therefore avoidance of early erection is essential. He gives his patients stilboestrol (the dose depending upon the child's age) for five or six days before entering the hospital and for one week after the operation. Operation is not performed until the patient states that he is unable to have an erection.

7 The nurse is also expected to take care of the psychology of the patient who is naturally shy on account of the congenital anomaly. She must create confidence in him that he is going to be a normal individual as a result of the operative procedure.

8 In actual practice it is necessary to explain to the parents the number of steps that are planned and the length of time necessary to complete the procedure. The possibility of the common pitfall of a fistula should also be mentioned to them stressing at the same time that the fistula is capable of being corrected after a minor operative procedure. If the patient or his guardian is given an idea at the outset that the operation is a time-consuming piece of work their co-operation can be counted upon than otherwise.

Choice of operative procedure—Now I come to the real problem faced by almost all of us, viz, the choice of a method of operation for any given case. Everybody is agreed that there are two reasons for correcting the deformity, (1) it interferes with the sexual function and (2) that the urinary stream splashes against the skin of the penis. The operation is designed to fulfill two purposes viz, correction of the ventral deformity and construction of the penile urethra. If the ideal is attained the penis is free from a ventral scar and the urethra is of adequate calibre and entirely free from the growth of hair. The prepuce is always redundant and hoodlike. This available skin has been very handy in providing a non-hairbearing skin for the formation of the urethral tube in the methods of Edmunds and Nesbit.

In all operations correction of the chordee is the first step. This should be done at an early age so that a normal growth of the corpora cavernosa constituting the shaft is facilitated. The essential part of this operation is excision of the inter-cavernous fibrous tissue. The following methods are available.

- (a) Making a transverse cut distal to the meatus, excising the fibrous tissue and suturing the cut longitudinally in the Heineke-Mikulicz fashion. This is very often found to end again in a ventral curvature.
- (b) Incising the skin on the ventral surface distal to the meatus in the midline exposing the intercavernous band and excising it in one strip. Slitting the Buck's fascia transversely so as to expose the body of the corpora cavernosa on either side and then uniting it by stretching the cuts longitudinally.
- (c) Edmund's operation constituting the 1st and 2nd stages.
- (d) Nesbit's operation (Fig I—1, 2, 3, 4). Here as in Edmund's the prepuce skin is used to cover the ventral surface of the penis denuded of its fibrous tissue but this is done in one stage. Sometimes the lateral ends of the transverse closure appear to involve too extensive amounts of skin making "dog ears". Eventually they have to be trimmed off. Sometimes the preputial skin may be found insufficient to cover the raw surface.

In all these methods the original meatus moves much further up than before. Penis is preferably kept hyperextended by passing a silkwormgut through the glans and stitching it to the abdominal wall. No diversion of urine is necessary for this step. A catheter is kept in the urethra to drain away the urine without spoiling the suture line.

Construction of the urethral tube. I divide all the operations for construction of the tube into four groups.

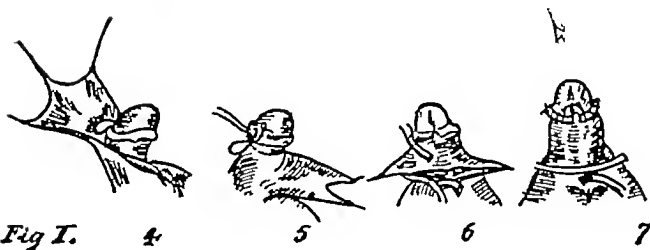
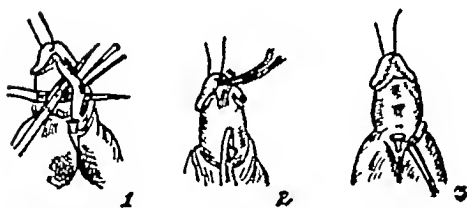
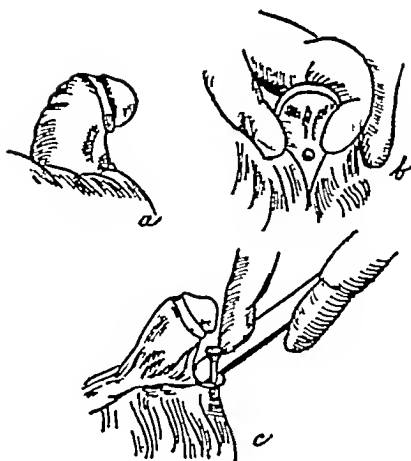
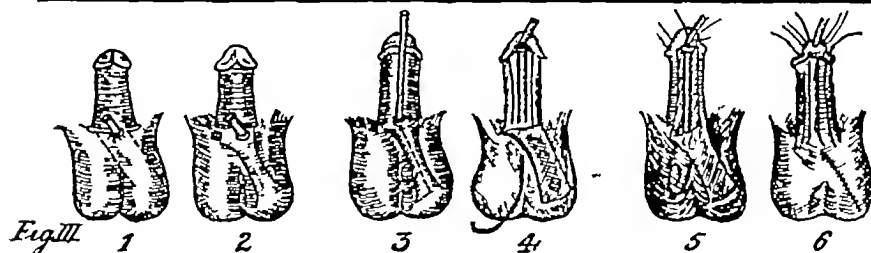
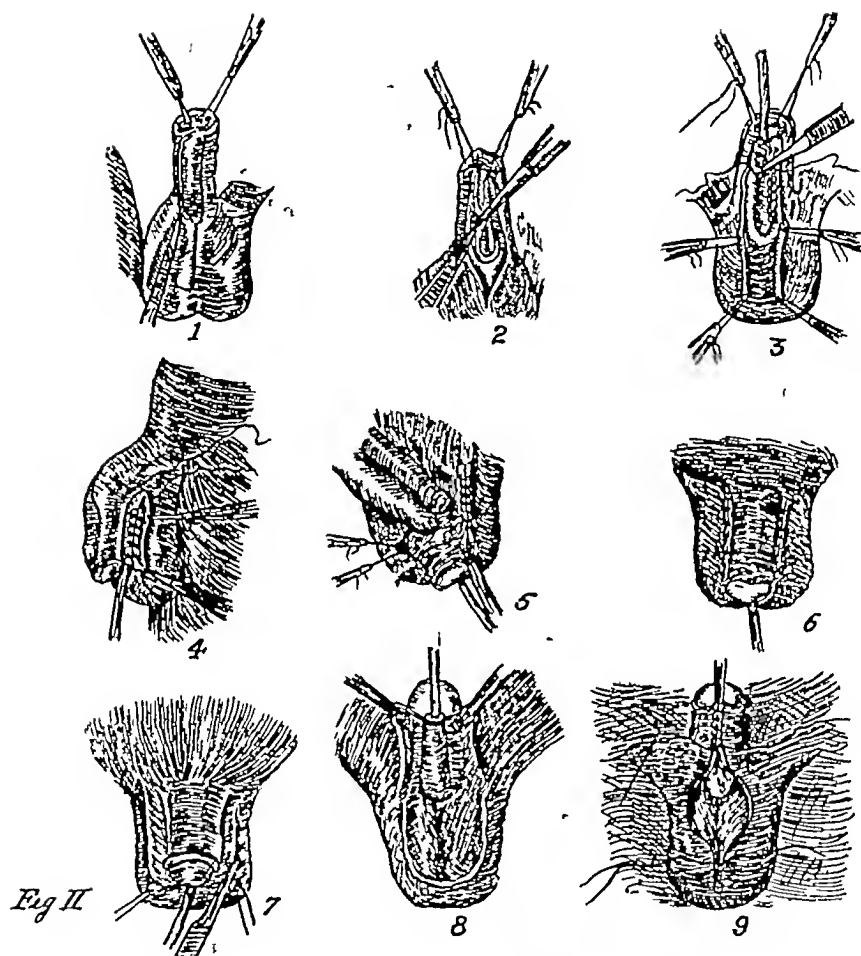


Fig I.

Fig I.



Figs II & III

Group 1—Here the urethral tube is made from the skin of the prepuce previously implanted on the ventral surface of the penis as in the methods of Edmunds or Nesbit. This tube is made either in the fashion of Duplay or Thiersch. The tube and the raw area on its either side is preferably covered by a pedunculated skin graft previously raised from the scrotum instead of by the adjoining skin from the penis which leads to too much tension on the suture line. Goodhope¹ (1945) (Fig. III—1, 2, 3, 4, 5) and Wehrbein⁶ of Brooklyn⁶ (1948) illustrate the use of the flap very well. There is much to be said in favour of this method as the urethra is lined by a nonhairbearing skin assured of its blood supply and the cover from the scrotal skin can be stitched in place without any tension on the suture line.

Group 2—In this group I include Bucknall's operation and his modification by Cecil¹³ in 1946, and also the method of Lowsley and Kirwin. In Bucknall's method the urethral tube is formed partly and in Lowsley and Kirwin's wholly from the scrotal skin which is a disadvantage. Cecil reports cases where stones had to be removed from the hairbearing urethra from a Bucknall's. So he has modified the Bucknall's operation in such a way that the tube is formed from the penile skin and then the shaft of the penis is stitched to the scrotum (Fig. II—1 to 9).

Group 3—The pouch operation of Ombredanne¹⁰ though described by him first in 1923 seems to have caught attention of the urologists in general only lately. No surgical textbook makes any mention of it. Lyle of New York (1928) advocates its use and says in its favour that the pouch urethra delivers the urine to the meatus without the possibility of leakage, there are no lateral edges to separate and it does away with the possibility of diverting the urine. In 1942 and 1944 Farmer⁶ and Muschat⁸ have reported favourably on its use and lately Goldstein¹¹ of Baltimore in 1946 has submitted a report of three successful operations by Ombredanne's method. One of them is a record case of a man of 29 who as a boy at the age of 12 was seen for penoscrotal meatus first in 1929 and after 36 operations over a period of 16 years the best result that could be obtained was that the meatus was brought to a point just above the penoscrotal juncture. This patient ultimately had a good result when operated upon by the Ombredanne's method. The technique of the operation is as follows:

1st Stage—(1) Placing the pursestring stitch, (2) Dissection and liberation of the flap, (3) Making the Y shaped incision. Passing the glans through the incision and fixation of the flap.

2nd stage—After a period of about 4 months. (1) Refreshening the edges and aesthetic touching up and excising the 'ears'. Here I must report one unfavourable view published by Wehrbein. He says that after an Ombredanne what is left in the penis is "an unsightly terminal bag and not a urethra"¹¹.

Group 4—I include the tunnelling operations in this group. Van Hook, Mayo Esser and Nove-Josserand are the older surgeons who advocated this method. Control of Haemorrhage in the tunnel was not satisfactory. The graft whether of the preputial skin or a free skin graft mounted on a catheter or of a material like a bit of ureter, appendix or a vein had its lining gradually destroyed and replaced by granulation tissue. Repeated dilatations were necessary to keep the

lumen patent Among the newer surgeons Levi⁸ reported in its favour in 1940 and very recently there has been an excellent article by Young¹⁴ and Benjamin of New York (1946) who are very enthusiastic in reviving Nove-Josserand's operation in a slightly modified fashion They straighten the penis and make a tunnel through it and the glans, and pass in the tunnel so created, a rubber catheter covered by a graft of skin removed from the medial side of the arm by means of a dermatome They insist on getting their cases in early infancy and report on ten cases It is to be noted that out of these ten cases the immediate result in seven was not satisfactory because these seven cases developed a fistula though the final result in 9 is good after secondary operations for closure of the fistulae

Operations by the methods of Goodhope or Wehrebein utilising scotal flaps to cover the newly formed urethral tube in Group 1 or Cecil's operation in Group 2 commend themselves to me as they seem to conform to sound principles of Surgery These methods involve operation in stages while the method of Young and Benjamin who use a flap from the medial side of the arm for the tube (Group 4 above) and finish the operation in one stage does deserve a trial

Drainage—The question of bypassing the urine has been tackled by different surgeons in different ways In the first stage of straightening the urethra it does not seem to be necessary as an indwelling catheter in the urethra works well In the next stage extremes of views prevail Charnock and Kiskadden of Los Angeles state that they have completely discarded the use of catheters or any type of artificial bypassing for whatever the precautions used it has been their experience that some urine will find its way in the operation field Indwelling catheter renders the urine infective and if no attempt is made to bypass the urine it remains sterile It is their practice to reconstruct the urethra down to the original opening allowing the child to void through the orifice until the urethral tube has become completely healed When healed, the urethra is calibrated and if found deficient in diameter a course of treatment by dilatation is instituted Joining the proximal and distal urethra requires a small flap Sinus formation is rather common and aggravating The method of closure consists of freeing the tissues undercutting the mucosa and passing a pursestring suture Edmunds also advocates that it is not necessary to employ diversion of the urine for his method of operation He goes to the extent of allowing the child to pass urine freely through the newly formed urethra It has been my experience in two cases that fistulae do form when the urine is not bypassed

Among the two methods of diversion viz, the suprapubic and the perineal the latter i.e., perineal urethrostomy is the method of choice as recent articles by Cecil¹³ (1946), Dodson¹⁸ (1944) and Young¹⁴ and Benjamin (1948) show that there are definite advantages in its favour Cecil describes a quick and easy way of establishing perineal drainage and refers to one complication viz, bleeding from the bulbous urethra The blood trickles through the distal newly formed tube and it is not often easy to distinguish whether the sutured tube or the perineal wound is bleeding In perineal hypospadias the hypospadiac opening serves for drainage until the urethra has been constructed to within half an inch of the opening Then a suprapubic cystostomy is done

and the perineal drainage is closed. When the urethra opens anterior to the perineum a perineal urethrostomy is the best method for drainage. When the operation is to be done in stages a permanent urethrostomy may be made by extending the incision in the urethra by half an inch and suturing the mucous membrane to the skin. This is not difficult in children where the urethra is near the surface. With this procedure it is not necessary to keep the catheter in place until the wound has healed. Consequently there is less danger of infection of the urinary tract and a repeated urethrostomy is avoided. The fistula is easily closed by separating the mucous membrane from the skin and suturing the opening with interrupted sutures. The premature passage of urine caused by stoppage of the perineal drainage tube is a frequent cause of infection and breaking down of sutures. This may be prevented by placing a silkworm gut suture around the urethra just in front of the urethrostomy and tying it just tightly enough to occlude but not cut through the urethra.

Davis² (1944) reports one ingenious way of bypassing the urine in a case of midscrotal hypospadias. He avoided cystostomy by continuing the new urethra backwards over the hypospadiac meatus to the posterior limits of the scrotum thus producing a small perineal fistula which could be easily closed at a later date. A reference to the figure in his article makes it easy to comprehend his idea.

Why surgical cure is unusually difficult—Wehrlein (1943) in his review answers the question briefly as follows. He points some handicaps which have to be faced. (1) The part is a passage of urine and also near the anus and therefore it is very difficult to maintain asepsis. (2) Blood supply is terminal and therefore collateral circulation cannot be counted upon. (3) We are attempting not only to correct a deformity but are also making a functioning mechanism, and (4) last but not least scarcity of experience. To quote his own example he himself working in two urological clinics in two different hospitals at Brooklyn had 21 cases in 15 years. Of these there were ten in the first 10 years. They ended mostly in failures. They were operated either by the technique of Duplay or Ombredanne and resulted either in fistulae or a unsightly terminal bag and not a urethra. Last 15 cases have been operated by using a flap and have shown a satisfactory result. In contrast to this Ombredanne is reported by Lyle¹⁰ to have done 250 cases without a failure.

Haematoma, tension on suture lines, infection and sinus formation and contraction of flaps are all incident to operation and each one of them is capable of being either prevented or eradicated.

Personal Cases—My personal cases are only five in number. 3 being hospital cases and 2 private patients. Case nos 1 and 2 were operated upon by Edmunds' method, No 3 by Bucknall's and Nos 4 and 5 have been dealt with by Nesbit's method and scrotal tubes have been raised and they are now due for the final stage operation. All the 5 cases have had penile hypospadias, more or less at the penoscrotal junction.

Case No 1 R. A. age 4 at the time of starting the treatment. Edmunds' 1st stage was done in September 1942 and 2nd stage in March 1943 at the G. T. Hospital. The third stage was done at the K. E. M. Hospital on 15th October 1943. Indwelling catheter in the

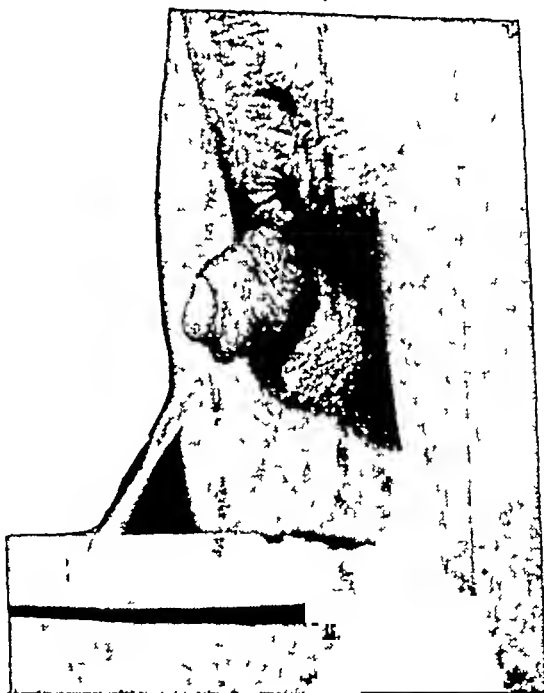
urethra kept for 3 days and no diversion employed as advised by Edmunds. A fistula developed. Readmitted on 31-3-1945 and the fistula repaired and this time not even the indwelling catheter kept. Patient was discharged but developed the fistula again after a few days, was again admitted on 6-5-45 and the fistula was repaired and this time he left with a normal looking penis, and passing urine from the tip of the penis. Recent followup shows that he has got a small fistula.

Case No 2 S B age 4. Edmunds' first stage done on 14-11-45, and 2nd and 3rd stages at four months' interval. After the last stage he developed a fistula. Fourth operation was undertaken to repair the fistula but this time in view of the experience of the first case a suprapubic cystostomy was done before undertaking the repair of the fistula. In spite of the diversion of urine the wound of the repaired fistula broke and now he has got a urethral tube of good calibre and full length but interrupted by a fistula which I propose to close.

Case No 3 S S age 11 was admitted in the K E M Hospital on 15-3-46. A suprapubic was done on 20-3-45 and a Bucknall's operation 1st stage was done on 8-4-1946. The 1st stage at the end of the operative procedure promised to be excellent but ultimately the wound on the left side for about 1/3rd in its length gave way. He was asked to attend the hospital after 2 months but he has not turned up.

Case No 4 B B age 15. A repair was attempted by another surgeon outside after a suprapubic cystostomy. The wound broke completely. After about nine months he was referred to me and was admitted in the K E M Hospital. I have done a Nesbit's operation and raised a scrotal flap and now I propose to reconstruct the tube. In this case I have to pass two comments (1) The preputial flap was found insufficient in length when the raw area on the ventral surface of the penis was covered by the same as was evident by tension in the transverse suture line. Ultimately the flap has taken well. (2) There has been great shrinkage of the scrotal tube and I am afraid I will have to raise a much wider one before attempting the final stage.

After reading this paper, at the time of going to the press, case No 4 has completed treatment and



has had excellent result. The idea of performing Goodhope's operation was given up as the scrotal tube had shrunk to a great extent. So a permanent perineal urethrostomy was done and a urethral tube was formed and the penis with raw area on either side of the tube was stitched to a bare area of the scrotum (Ceel's method, Fig 3). 3 months later the penis was liberated from the scrotum. The patient now passes urine from the tip of the penis (Fig 4). The suprapubic scarring seen in the picture is due to the operation he has had outside the K E M Hospital before he came under my care.

Case No 5 B A came to me for a penoscrotal meatus and marked ventral deformity which has been satisfactorily corrected by a Nesbit's in July 1948. He has developed 'dog ears' as Nesbit puts it at the ends of the transverse suture which can be excised. A tube has been raised and I will not be surprised if this too shrinks considerably before he is due for the final stage.

CONCLUSION AND SUMMARY

1. All available literature on the subject, specially from 1941 onwards, has been reviewed, and an attempt is made to evaluate the different methods. One feels that it is best to attempt a cure by doing an operation like the Nesbit's and providing a cover for the ventral surface of the phallus by raising a scrotal tube turned at the final stage into a flap or by doing Ceel's operation. At the same time one is not blind to the fact that revival of the old tunnelling operation of Nove-Josserand in the hands of certain surgeons is giving promising results. Perineal urethrostomy seems to be the most practical way of diverting the urine.

2. Despair and disappointment at the final result seems to be the lot of majority of the surgeons. Yet in view of the recent advances it can be safely said that there is no reason to adopt such an attitude. In reference to this I may cite the case of Goldstein¹¹ once again, where he had a success after 36 failures during a period of 12 years. Of course it is an extreme example but it definitely points the right way to the disappointed surgeon. In spite of repeated giving way of wounds, infections and sinus formations there will always be a way to correct the deformity.

REFERENCES

- 1 Use of wire in the repair of hypospadias. Goodhope: Jour of Urology 54 471 473 Nov 45
- 2 New operation for mild scrotal hypospadias. Davis: Jour of Urology 52 340-345 Oct 44
- 3 Experiences with Ombredanne Operation. Muschat: Jour of Urology 51 437 438 Apr 44
- 4 Hypospadias. Wehrlein: Jour of Urology 50 335 340 Sep 43
- 5 Hypospadias. Charnock and Kiskadden: Jour of Urology 49 444-449 Mar 48
- 6 Hypospadias. Farmer: Surgery 12 402-470 Sept 42
- 7 Hypospadias. One stage operation B. J. S. 29 84-92 July 41
- 8 Operation for penoscrotal hypospadias. D. Levi: Lancet 2 777 Dec. 21 1910
- 9 Plastic procedure for correction of Hypospadias. Nesbit: Journal of Urology 45: 699 702 May 41
- 10 Ombredanne's operation. Lyle: Annals of Surgery 513 Oct 1939
- 11 Modified Ombredanne operation for penile hypospadias. Goldstein: Jour of Urology 56 746-750 Dec 46
- 12 Nursing care in Surgical repair of Hypospadias. Iucelle Wright & Prince 46 686 689 Oct 46 in American Journal of Nursing
- 13 Repair of hypospadias and urethral fistulae. Ceel: Jour of Urology 56 237 242 Aug 40
- 14 Repair of Hypospadias with free inlay skin graft. Young and Benjamin: S. G. O. 439 452 April 48

BOOKS

- 15 Year-Book of Urology—1947. Higgins on use of Stilboestrol reported in Cleveland clinic
- 16 Urology—Cabot
- 17 Urology—Lowsley and Kirwin
- 18 Urology—Dodson
- 19 Carson's Op. Surgery
- 20 Rowlands & Turner—Op. Surgery

INCIDENCE OF PEPTIC ULCER AS STUDIED BY RADIOLOGICAL METHOD

by

DR J C PATEL, MD (Bom) MRCP (Lond)

„ **L H ATHLE**, MB, BS, (Bom.), DMR E (Eng)

„ **V S PRAYAG**, MD (Bom) and

„ **M S VARAVDEKAR**, MB.B.S

Dr V S Prayag gave a preliminary report on the Incidence of Peptic Ulcer as judged by roentgen examination of the gastro-intestinal tract in 800 cases

The procedure adopted in the particular study consisted of a detailed clinical study with particular stress on the full history of the patient. The patients were then referred to the x-ray department without any special preparation except starvation on the morning of the examination. A complete study of the stomach and duodenum and the rest of the tract was done by the department. Fluoroscopy was routinely employed and films were taken only when absolutely necessary. This had to be done on account of the paucity of films.

Gastric analysis and stool examination were obtained in as many cases as possible. Attempt was made to follow these patients up. Detailed reports of the findings were obtained whenever operative treatment was given.

Dr Prayag then read out the various tables in which the findings were analysed.

Dr Athle in his remarks pointed out that the stomach was washed out in cases of Pyloric Obstruction before a roentgen examination was attempted. Whenever there was ileo-coecal or colonic disease the barium meal was supplemented by barium enema examination.

He then discussed the diagnostic value of x-ray study in cases of Peptic Ulcer and pointed out the causes of incorrect diagnosis inspite of careful examination. The need for co-relating the clinical and radiological findings was great in this group of cases where a definite diagnosis could not be established on x-ray examination alone.

He discussed at length the methods of diagnosis of chronic appendicitis and pointed out the fallacies encountered with in certain types of cases.

Dr J C Patel emphasised the need of radiological assessment of the incidence of peptic ulcer. This has been done in other countries several years ago. Post-mortem records alone do not show the correct incidence. Operative records also are inadequate in conditions which are mainly treated non-surgically. He compared the available figures of incidence of peptic ulcer in the literature in the various countries and compared them with the work in hand.

Dr DeSa asked about the diagnosis of T B Intestine by barium meal methods in early cases.

A paper read before the 84th meeting of the Seth G S Medical College and K E M Hospital Staff Society on 14th Aug 1948 with Dr N K Sahasr in the chair.

Dr Athle in his reply stated that most of the cases came late and diagnosis was easy in these. He gave the criteria of diagnosis in early cases.

Dr N K Sahuar asked about the incidence of Chr Amoebiasis in the cases of Chr Appendicitis. He drew attention to the significance of their co-existence.

Dr J C Patel agreed with Dr Sahuar that it was important to look for Chr Amoebiasis in the cases of Appendicitis but as the stool examination was done only in some of the cases in this series, he could not give the percentage of positive stools in the cases diagnosed as Chr. appendicitis.

EXPERIENCE WITH MALIGNANT LESIONS

by

DR V M KAIKINI, BA, FRCS (Edin)

In contrast to the diseases like tuberculosis, typhoid, malaria and others which are due to poverty, ignorance, insanitation, etc., malignant disease prevails as much or perhaps more among people living among the comforts of modern civilisation. Malignant disease although common in old age may occur in any period of man's life. It starts very insidiously and is painless in the early stages. Presence of pain, cachexia, and secondary glands indicate that the disease has attained an advanced stage. Sudden loss of function in an otherwise healthy organ must make one suspicious of malignancy. Radical removal by operation in the early stages is the only treatment which may cure the disease.

The following is the list of operations personally done for malignant disease during the course of the last twenty-three years

	<i>Description of the case</i>	<i>Operation</i>	<i>Result</i>
1	Sarcoma of the Sphenoid invading the pituitary fossa, One case	Partial removal	Patient died
2	Meningioma—One case	Complete removal	Recovery
3	Sarcoma right eye-ball—One case	Enucleation	Recovery
4	Malignancy of superior Maxilla—12 cases	Excision of maxilla	Operative death, one—No recurrence in two. Recurrence in other cases
5	Malignancy of Mandible—Two cases	Excision of the mandible	No operative deaths but recurrence in both
6	Naso pharyngeal tumour—Three cases	Radical excision	Recovery in two. One death. Recurrence in one
7	Carcinoma Cheek—12 cases	Excision	Recurrence in one case
8	Carcinoma of Tongue, about 25 cases 8 of these were on the posterior third	Excision	No operative death. Recurrence in all posterior third cases
9	Carcinoma of the Larynx—Nine cases	Complete larygectomy	Three survived the operation
10	Carcinoma of the Thyroid—Two cases	Complete thyroidectomy in one case	Fatal
11	Carcinoma Breast—Forty cases	Radical mastectomy	Majority recurred
12	Oesophageal carcinoma—Two cases advanced	Oesophagectomy in one case	Fatal
13	Carcinoma Stomach Seven cases all advanced	Gastrectomy	All fatal
14	Carcinoma Colon—Five cases	Colectomy	One operative death. Recurrence in two
15	Carcinoma Rectum—Seven cases	Excision of rectum by transsacral route in 4 cases and by vaginal route in three	One operative death. Recurrence in two

A Paper read before the 86th meeting of the Seth G. S. Medical College and K. E. M. Hospital Staff Society, on 9th October 1948 with Dr J. N. Karande in the chair

	<i>Description of the case</i>	<i>Operation</i>	<i>Result</i>
16	Carcinoma of Bladder trigone	Portion of trigone removed by Volcker's method	Complete recovery no recurrence
17	Carcinoma Prostate	Two cases Operated by Young's radical method	Died after 6 months
18	Cancer of Penis About 30 cases	Radical or partial amputation	Good result
19	Cancer of Testis—One case	Radical removal	No recurrence
20	Sarcoma Shoulder joint	Interscapule thoracic amputation	Good result.
21	Carcinoma Uterus—Three cases	Panhysterectomy in two cases	One case fatal, other recurred after one year
22	Carcinoma Gallbladder One case	Radium treatment Cholecystectomy	Complete recovery Fatal

The record of 168 cases of malignant disease is given along with the treatment and results. All the cases except one were treated by operation. Only one case, carcinoma of uterine cervix an inoperable one. Luckily the patient improved and has had no recurrence of the trouble up to now.

Critical Notes and Abstracts

AUREOMYCIN

Finland, Collins and Paine report clinical trials with aureomycin in a group of 100 patients with a variety of bacterial infections and sensitivity tests of bacteria to aureomycin, carried out with 186 strains of bacteria isolated from the patients in the Boston City Hospital. Hemolytic streptococci, pneumococci, gonococci and meningococci were almost completely inhibited by aureomycin in concentrations of 1 microgram per cubic centimeter. Staphylococci and most strains of gram-negative bacilli, including typhoid and other *Salmonella*, were inhibited by large doses.

There appeared no significant tendency for development of strains resistant to aureomycin either *in vitro* or *in vivo*. Aureomycin was absorbed rapidly and appeared rapidly in urine excretion. Four or five cases of typhoid in children who had positive blood cultures before treatment, showed negative cultures after two to three days of aureomycin therapy. In the 100 patients treated, results were good in 64, doubtful in 28, and failed in 15. Toxic effects were minimal and infrequent.

The authors concluded that aureomycin has definite antibacterial activity against many bacteria including cocci and bacilli and that it may prove useful in infections by organisms that are resistant to penicillin or streptomycin. Treatment by mouth was generally effective. It has been suggested in other studies that aureomycin may find its major field of usefulness in rickettsial infections or with viruses of the psittacosis-lymphogranuloma venereum type. The present study indicates that aureomycin deserves a more extended clinical trial with many varieties of bacterial infections.

(Finland, Maxwell et al. Boston, Mass. Aureomycin: A New Antibiotic. Results of Laboratory Studies and of Clinical Use in 100 Cases of Bacterial Infections. *Journal of the American Medical Association* 138: 940-949, November 27, 1948.)

STREPTOMYCIN RESISTANCE TO TUBERCLE BACILLI

Wolinsky, Reginster and Steenken report the results of streptomycin sensitivity tests on tubercle bacilli isolated from a large group of patients before, during and after treatment with various drug dosages. The organisms were recovered from various body fluids, cultured and a representative sample of many colonies was used in the sensitivity tests. Cultures of tubercle bacilli isolated from 47 patients before treatment, were uniformly sensitive to one-tenth μm per cubic cm. Of this group 4.5 percent showed resistant cultures after four weeks of therapy, 12.5 percent showed resistant cultures after six weeks therapy, 23 percent after eight weeks of therapy and 37 percent were resistant after 12 weeks of therapy.

In general, it was believed that streptomycin resistance is a relatively long-lasting characteristic of tubercle bacilli both *in vitro* and *in vivo*. However, serial cultures from two patients reverted from drug-resistant to drug-sensitive. The authors considered that until a more effective method to eliminate drug resistance becomes available,

the best plan for limiting development of streptomycin resistant strains of tubercle bacilli, was to limit the course of treatment to from four to six weeks at which time 75 percent of the cultures may still be expected to be sensitive

(Wolinsky E et al Trudeau Sanatorium Trudeau N.Y. Drug Resistant Tubercle Bacilli in Patients Under Treatment with Streptomycin American Review of Tuberculosis LVIII 335 343 September 1948)

NITROGEN MUSTARD THERAPY IN BLOOD TUMORS

Block, Spurr, Jacobson and Smith carried out a histologic study of lymph nodes, bone marrow and spleen in a group of patients of neoplastic disease of hematopoietic tissues. Studies were made before and after nitrogen mustard therapy. Studies included patients with Hodgkin's Disease, Lymphosarcoma, Giant Follicular Lymphoblastoma, Chronic Myelogenous Leukemia, Lymphatic Leukemia, Multiple Myeloma, and Metastatic Carcinoma.

The authors concluded that bone marrow exhibits a slight increase in degeneration 24 hours following an injection of nitrogen mustard. This is followed by an atrophic phase and regeneration and a hyperplasia within 30 days after the first injection. Lymph nodes in Hodgkin's sarcoma showed little histologic change following therapy. In lymphosarcoma and lymphatic leukemia a fairly intensive lymphatic destruction occurred. In multiple myeloma, myelogenous leukemia and metastatic carcinoma observation failed to demonstrate any clinical or histologic change following nitrogen mustard therapy.

The authors believe that in general, nitrogen mustard exerts its principal cytotoxic effect on the smaller lymphocytes, myelocytes, erythroblasts, and megakaryocytes. Reticular and plasma cells were more resistant. The authors considered that methods of therapy of neoplastic diseases of the hematopoietic tissues, which rely on the destruction of the more susceptible cells are doomed to failure because of the reserve of immature reticular cells which serve as a source of regeneration and carry on the malignant properties of the disease.

(Block, Matthew et al University of Chicago Chicago Ill. Histopathologic Effects of Nitrogen Mustard Therapy Upon Normal and Neoplastic Hematopoietic Tissues American Journal of Clinical Pathology 15 671 689 September, 1948)

SPHENOPALATINE GANGLION BLOCK

Dr J Lewis Amster reports the treatment results of sphenopalatine ganglion block for the relief of pain in vascular and muscular spasm. A variety of cases were treated including a large number of patients with lumbosacral and sacroiliac pain. Other conditions included migraine, acute torticollis, ureteral colic, herpes zoster and dysmenorrhea. In the 327 injections given, no significant toxic results occurred. Various anesthetic agents were used, such as cocaine, nupercaine, and panto-caine.

All the anesthetic substances were found suitable for continuation with the exception of cocaine to which two patients reacted poorly. The use of cocaine has been discontinued. Relief of pain and spasm was noted in approximately 90 percent of the patients treated. In many cases a spectacular relief of pain and spasm occurred after one injection. It was noted that the shorter the duration of the condition, the more rapid was the response to treatment. Investigation of this

treatment method is still being continued individually by a group of physicians in the New York area

(Amster J Lewis New York NY : Sphenopalatine Ganglion Block for the Relief of Painful Vascular and Muscular Spasm with Special Reference to Lumbosacral Pain New York State Journal of Medicine 48 2475 2480 November 15 1948)

LIVER DYSFUNCTION IN INFECTIOUS MONONUCLEOSIS

A study of hepatic dysfunction associated with infectious mononucleosis has been recently carried out by Peterson in a group of 41 patients who had typical blood findings of infectious mononucleosis. A battery of liver function tests applied to the whole series, showed that 55 percent of the patients had a moderate to severe hepatic functional involvement, or hepatitis. Clear cut signs of hepatic functional impairment was evidenced in three or more tests of the ten tests used in the study. In none of the group of 40 patients were there any serious complications and in those pointing to hepatic dysfunction, a return to normal occurred in a short period of time.

In general, those patients with hepatitis appeared to have a slightly more severe form of infectious mononucleosis. The liver function disturbance pointed to the presence of both hepatocellular and cholangiolar injury. The author considered that the evidence presented tends to refute the theory that jaundice in infectious mononucleosis is due to an extra hepatic obstruction of the common duct by enlarged lymph nodes.

(Peterson Ralph E Madigan General Hospital Ft Lewis Wash Hepatic Dysfunction in Infectious Mononucleosis With Review of the Literature Journal of Laboratory and Clinical Medicine 33 1258 1270 October 1948)

PSYCHOTHERAPY TO THE INTERNIST

Reviewing the value of psychotherapy to the internist, Thomas emphasized the failure to accept a responsibility for such therapy by a large group of internists. It was pointed out that many internists felt that the psychologic aspects of diseases were felt to be someone else's obligations. The author suspects that such physicians are consciously or unconsciously attempting to avoid involvement in the complex and illusive aspects of human nature.

These men were considered generally inept in dealing with personalities and frequently tend to consider psychiatrists unnecessary except for psychotic patients. It was noted that many internists were themselves tremendously prejudiced against the admitting of a formal psychologic or psychiatric approach to medical patients on the basis that the therapeutic concepts involved had not been scientifically substantiated.

Illustrative cases are presented showing breaks in technic in which the physician himself is responsible for the subsequent development of neurotic or psychoneurotic symptomology. The conversation of the doctors with their patients was demonstrated to create erroneous impressions in the patient's mind, permitting an ever increasing fixation of conditioned invalidism and underlying nervous instability. Several helpful techniques in psychotherapy are discussed.

(Thomas Henry M Jr Baltimore Md What Is Psychotherapy to the Internist? Journal of the American Medical Association 138 878 880 November 20 1945)

LOCAL INJECTION OF PENICILLIN IN ACUTE CIRCUMSCRIBED INFECTIONS

According to Kaplan and Rabin acute infections may be divided into two clinical types (1) acute infections which do not cause death of tissue, such as septicemia and cellulitis and (2) acute infections causing suppuration and death of tissue, as seen in boils and carbuncles. In the absence of suppuration or death of tissue, acute infections are superficial and spread over a wide area, relatively unconfined by a wall of inflammatory tissue. In contrast, where suppuration and death of tissue have occurred, a localized area of gangrene is surrounded by a zone of granulation tissue which separates the living from the dead tissue and which circumscribes the infection and prevents its spread, but which also acts as a barrier to a free circulation into the diseased area. Because of these differences, the response to any form of therapy is not the same in these two types of acute infection.

It has been shown that the results of parenteral therapy with penicillin may vary considerably in the two types of acute infection. The results in acute infections in which there is no death of tissue are quite dramatic, while in acute localized infections, with suppuration, the results are at times discouraging.

It seemed to the authors that the most suitable method of administration of penicillin in acute localized infections should be direct injection into the infected area. By this means a high concentration and a deep even distribution of the drug at the point where it was needed could be assured.

The authors inject 8 cc of distilled water into a bottle containing 100,000 units of penicillin, making a dilution of approximately 33,000 units to the cubic centimeter. The size of the lesion determines the amount of the solution to be injected. Too much tension in the infected area may break down the barriers that the body has set up to localize the infection and must be avoided. Small lesions require 0.5 to 1 cc at each injection, while larger ones, such as a carbuncle, may require 4 cc, or even more. Approximately 1 cc is given for the average localized abscess. The required amount is aspirated from the bottle containing the solution and the remainder kept in the ice box for injection on the following day, as the potency of refrigerated penicillin in solution is maintained for approximately 24 hours.

The injection is made with a 24-gauge hypodermic needle into the most dependent area of the abscess. Without entirely removing the needle, the operator makes several injections into different areas of the lesion in order to insure an even distribution of the drug. Usually spontaneous evacuation of the pus occurs during the injection, depending upon the stage of the infection. If the abscess is superficial and pointing, this occurs practically all the time. In cases in which the abscesses are fluctuant, they are aspirated with a larger needle immediately before the injection of the penicillin solution. In carbuncles the injections are made between the areas of pointing, and the needle is usually inserted deeper than in the localized abscesses.

The authors have used the local injection of penicillin in over 800 cases of acute localized infections. Their experience has demonstrated that it is safe, effective, and economical. There were no complica-

tions Following injection directly into the affected tissue, there is almost immediate improvement and recovery is established in a few days. Extremely gratifying, in addition to the rapid healing time, is the cosmetic result obtained. There is practically no loss of skin and no deforming scars are seen as usually found following surgical intervention. The authors do not believe, however, that this form of therapy should be used in all types of acute localized infections. It should be reserved for the more serious ones and for the lesions so located that surgical procedures may produce a bad cosmetic result. It is useful when surgical intervention has proved to be inadequate.

It is not recommended for the treatment of the cellulitides, for infections in the dangerous areas of the face, or for bone felons. Surgical judgment must be exercised in each individual case.

(Kaplan I W. New Orleans La. and Rabin, H. *Annals of Surgery* 127 1202 1206 June 1948
The authors are connected with the Touro Infirmary and the Charity Hospital of Louisiana at New Orleans.)

INTERNATIONAL TUBERCULOSIS PREVENTION

Under the sponsorship of the United Nations International Children's Emergency Fund and the Danish, Norwegian and Swedish Red Cross, a program for tuberculosis control on an international basis is being established.¹ The program which is to be carried out in war ravaged countries of Europe envisages examination of 50,000,000 children and adolescents under 18 years of age. An estimated 15,000,000 of these children will be found to need and will be given BCG vaccine. The bulk of the funds needed (\$4,000,000) will be contributed by UNICEF and additional sums are expected from other cooperating organizations.

The World Health Organization will provide technical advice and assistance. "Joint Enterprise" agreements will be signed between the sponsors and the Ministry of Health of each participating country. Medical teams for actual work will be assembled in each country composed of nationals and medical personnel supplied by the sponsoring agencies. Fresh vaccine and tuberculin will be supplied by the Danish State Serum Institute until each country is able to supply its own. Tuberculin intradermal or patch tests will be performed on all children and positive reactors will be vaccinated with BCG. Presumably BCG has protective value for several years.

Technical directions of the program is being entrusted to Danish, Norwegian and Swedish personnel because these countries have highly developed the techniques of mass vaccination with BCG during the past 20 years ("The tuberculosis death rate in Denmark in 1947 was 80 per 100,000 inhabitants"). Death rates in some of the countries to be included in the program are at least ten times the Danish rates. Joint enterprise agreements have already been signed in five countries—Finland, Hungary, Czechoslovakia, Poland and Yugoslavia. In Central Europe alone, as of July 1, 1948, more than 2,000,000 persons have been tested and over 600,000 vaccinated. China, Greece, and Italy, as well as other countries of Asia and the Western European countries, are being considered for extension of the programme.

The sponsors of this campaign, realizing that vaccination alone is not sufficient, consider other measures necessary for success to be

expansion of public health services for detection of new cases of tuberculosis, furnishing of increased number of beds for isolation purposes and training of more adequate numbers of personnel. The program is truly international in that neither national borders nor political, racial or religious discrimination will interfere with the extension of the program to the war ravaged areas where greatest need exists.

(¹ 'The What, How and Why of the International Tuberculosis Campaign' Public Relations Office International Tuberculosis Campaign Puggaardsgade 2, Copenhagen V, Denmark.)

BLEEDING PEPTIC ULCER

Fisher and Zukerman present 57 consecutive cases of bleeding from the upper gastrointestinal tract. The series was chosen to include all cases of initial or repeated hemorrhage from peptic ulceration which came under their supervision. The diagnosis in each case was compatible with either gastric or duodenal ulcer as shown by x-ray and/or by the clinical, physical and laboratory findings, there were no deaths in the series. There were 39 patients with duodenal ulcer and 19 with gastric ulcer, giving a ratio of 2.05 to 1.

The authors conclude that hemorrhage from peptic ulceration may take place at any age but it occurred more frequently in the fourth and fifth decades of life in the series. Bleeding from the upper gastro-intestinal tract as a result of benign ulcers occurs more frequently in men than in women. In this series there were 42 males and 15 females, a ratio of 2.8 to 1. Body build was not a pertinent factor in the occurrence of ulcer nor was it a factor in predisposition to hemorrhage in the cases reviewed. The authors strongly advocate that patients with bleeding from the upper gastrointestinal tract not be x-rayed until at least two weeks have elapsed after the onset of their hemorrhage because they believe that undue manipulation of the abdomen might precipitate severe hemorrhage at the time and that fluoroscopy carried out without manipulation and x-rays taken at the time of hemorrhage frequently fail to show any gastrointestinal lesion.

It was stated that factors precipitating gastrointestinal hemorrhage are (1) upper respiratory infections, (2) alcoholic beverages, (3) emotional disturbances, (4) dietary indiscretions and overwork. It was confirmed in the authors' series that the period from October to March is the time interval during which most hemorrhages from benign benign ulcer occur.

In outlining the management of upper gastrointestinal hemorrhage the authors place strong emphasis upon early feeding and large amounts of blood when indicated. They state that continuous and massive blood transfusions are not only life saving but innocuous. The most common symptoms at onset of gastroduodenal hemorrhage, in order of frequency of occurrence in the authors' series, are pallor, tarry stools, emesis of dark blood, weakness, severe epigastric pain relieved by alkali, nausea and syncope. The clinical picture at the onset of gastroduodenal hemorrhage varies according to the amount of blood lost.

In their final conclusions the authors list the following factors as those which determine the mortality in bleeding peptic ulcer: (1) it has been noted that there is a much lower mortality in bleeding ulcers in the female. (2) The age factor is one of the most important in determining the outcome for the patient, most deaths occurring after

the age of 45 (3) There is a definite higher incidence of deaths from first hemorrhages (4) Antecedent dyspepsia or ulcer-like symptoms definitely give a worse prognosis for bleeding ulcer patients It has been suggested that in those without previous ulcer symptoms the bleeding is due to a superficial ulcer or erosion rather than to a deep ulcer (5) Arteriosclerosis is stated to be a definite factor in the prognosis since the older patients bleed from ruptured, stiff vessels which do not retract and tend to stop bleeding (6) A patient showing a blood urea nitrogen of 100 mg percent or more or those patients in whom the loss in cell volume exceeds 50 percent the prognosis is definitely worse (7) Hypertension (8) Erosion into the pancreas and bleeding from granulation tissue in the base of the ulcer have been stated to be definite factor in giving a worse prognosis in these cases

(Fisher, Ralph Lee Riverside Clinic, Detroit Mich and Zukerman, Morris, "Bleeding Peptic Ulcer" *American Journal of Medicine* 5: 508-517 October 1948)

DIAGNOSIS AND TREATMENT OF ANEMIA OF THE NEW-BORN

Wiener, in discussing the hazards of abruptio placentae and placenta previa to the newborn who may be suffering from a dangerous anemia due to occult hemorrhage from the placental or umbilical vessels, presents two such cases and compares them with a third case of erythroblastosis It is the author's opinion that cases of unapparent hemorrhage from the fetal surface of the placenta are often treated like erythroblastotic infants, whereas the amount of blood injected should be sufficient to correct the reduction in blood volume in the former cases

In the first case related the mother was Rh positive and delivery was by Caesarean section, due to central placenta previa and noted weak cord pulsations Because of these facts, it was thought the pallor and weakness in the infant might be due to occult hemorrhage from the placenta A transfusion of 120 cc of citrated group A blood was given and the infant improved Oxygen had to be administered even after transfusion as the infant exhibited rapid shallow respirations On the following day 60 cc of blood was given and improvement was such that oxygen therapy was discontinued

In the second case labour was normal and the mother was known to be Rh positive Although the diagnosis of erythroblastosis fetalis seemed to be excluded by the facts that the infant was the first born and the mother Rh positive, the true nature of the condition was not fully appreciated The infant was given oxygen therapy and vitamin K Following 100 cc of blood transfused to the infant from the mother, there was a slight improvement, but a few hours later the infant expired The author points out that had this patient been seen after Case 1, the true nature of the condition might have been recognized and the infant might have been saved by more energetic transfusion therapy

In the third case presented the patient was extremely pale and feeble at birth Much mucus was aspirated from her throat and an immediate blood count showed a hemoglobin concentration of only 58 percent After a total of 90 cc of group A, type Rh blood were transfused into the infant, she died and could not be revived At postmortem examination the characteristic findings of erythroblastosis were noted The author states this case to be unusual because antenatal

tests repeated at intervals upto two weeks before delivery failed to reveal the presence of any Rh antibodies, yet the infant proved to be erythroblastotic

The author explains these findings by postulating some defect on the fetal side of the placenta, appearing during the two-week interval between the last antenatal Rh antibody titration and the delivery of the patient. The leakage of the fetal blood into the maternal circulation would account for the sudden reappearance of Rh antibodies in the maternal serum. Moreover, a slow ooze of fetal blood from such a placental defect could also account for the extreme anemia and shocklike condition of the infant at birth. The author concludes that it is important when erythroblastotic babies are born with extreme anemia and shock to consider the possibility that the anemia may be due not merely to hemolysis but also to actual blood loss through a placental defect.

(Wiener, Alexander S. Brooklyn N.Y. "Diagnosis and Treatment of Anemia of the Newborn Caused by Occult Placental Hemorrhage" American Journal of Obstetrics and Gynecology 56 717-722 October 1948)

ENTEROGASTRONE IN THE TREATMENT OF PATIENTS WITH DUODENAL ULCER

Sandweiss et al report a study on 48 private ambulatory patients all of whom had roentgenologically proved duodenal ulcers, and 90 percent of whom were selected for enterogastrone therapy because they failed to respond to the usual conservative diet-antacid-antispasmodic regimen. In summary, the authors state that enterogastrone was administered parenterally to 42 patients with proved chronic duodenal ulcers. The injections were given six, five or four times weekly during a period of three months (an average total of 79 injections). The immediate clinical results were disappointing, since only 55 percent of the patients had symptom-free intervals. Twenty-three patients (55 percent) had symptom-free intervals during the three month period of parenteral enterogastrone therapy.

After the course of parenteral therapy was completed, the 23 patients were given enterogastrone tablets orally. Sixteen, or 70 percent, of these patients presented symptoms of recurrent ulcer within one year after the institution of parenteral therapy. Clinical results with parenterally administered enterogastrone were compared with those previously obtained by one of the authors with diet-alkali regimens and with other parenterally administered products (vaccine, histidine, emetine, "enthelone" and distilled water injections). The comparative results indicate that (a) treatment with enterogastrone failed to produce more satisfactory results than the other therapeutic regimens, either in its immediate effect on symptoms or in its remote effect on recurrent attacks within one year, and (b) the lowest percentage of relapses within one year occurred among those patients who followed the usual conservative dietary regimen.

Thirty-three patients had a full three month course of parenteral enterogastrone therapy (an average total of 80 injections). Only four of the patients (12 percent) were still symptom-free 14 months after completing the three month regimen. The remaining patients had either not had a symptom-free interval at the end of the three-month period or had subsequent recurrences if they became symptom free.

The authors were of the opinion that the enterogastrone they employed, when administered parenterally during a three-month period (even if followed by oral administration of enterogastrone), does not produce "immunity" against recurrent ulcer. The authors are discontinuing the use of enterogastrone clinically for the present, since it is their opinion that (a) enterogastrone as commercially available at present is not to be considered a routine therapeutic medicament for peptic ulcer, and (b) further intensive studies on the physiologic and biochemical aspects of enterogastrone concentrates are essential to produce a better product.

(Sandweiss David I Detroit Mieh Sugarman Marcus H and Lockwood Bruce C. Enterogastrone in the Treatment of Patients with Duodenal Ulcer. *Journal of the American Medical Association* 138: 552-557 October 1948.)

CLINICAL PROBLEMS IN PENICILLIN SENSITIVITY

Peck et al describe some of the forms of penicillin reaction which they encountered, evaluate the diagnostic and prognostic significance of the penicillin cutaneous test and present their experiences with penicillin desensitization. Of the several penicillin sensitivity tests in use, the authors consider the most important one to be the delayed reaction to the intradermal injection of penicillin. When performed with 2,000 units (1-2 mg of crystalline penicillin G in 0.1 cc of isotonic solution of sodium chloride) and readings made 48 hours later, the test offered a reliable index of penicillin sensitization in the experience of the authors.

The reaction is characterized by an area of erythema which is usually associated with edema or infiltration. The largest diameter of the area of reaction may not be reached until three to five days after testing and the lesion may persist for a week or longer. Local pruritus is a common accompaniment of the reaction to the test. These workers found the patch test of doubtful value as an index to general penicillin allergy, since the test yielded negative results except in persons with pronounced sensitivity. The immediate intradermal cutaneous test was also found lacking. All of the reactions in the authors' series were negative, even on 10 patients in whom an eruption of the urticarial type had occurred as a result of penicillin treatment.

In summarizing their report on cases treated and observed in this study, the authors state that 406 adults and 93 children were tested with penicillin and trichophyton. Of 276 adults who had never had penicillin, 15, or 5.4 percent, reacted "spontaneously" to the penicillin cutaneous test. Of 108 men, 11, or 6.5 percent reacted positively, of 108 women four, or 3.7 percent showed a positive reaction. Of 65 children, none reacted positively. The "spontaneous" reaction caused by penicillin sensitivity was three times as frequent among those patients who had a positive trichophyton reaction.

Of 180 patients who received penicillin, 82 had cutaneous eruptions. Of these eruptions, 25 were of the urticarial serum-sickness-like type, seven were of the erythematovesicular, trichophytid type. In 34.2 percent of all men eruptions developed, whereas they occurred in only 8.8 percent of women. In this group, all 17 positive reactions to penicillin cutaneous tests occurred in men, or 18.4 percent of all patients. Of the 25 patients in the group with urticaria 21 were men and four women. Of these patients, 10 had a positive reaction to the

cutaneous penicillin test, and four had a positive trichophyton reaction, all were men. A previous instance of fungous disease is not considered to play a role in this form of induced sensitivity. The seven patients with the erythematovesicular type were men, each of whom had positive reactions to both the penicillin and the trichophyton test. The previous occurrence of fungous disease, which gave rise to penicillin sensitivity resulting in a "spontaneous" positive reaction to penicillin is considered the basic mechanism of this type of sensitivity.

The authors conclude that the delayed reaction to the penicillin cutaneous test is of practical value in the diagnosis of "spontaneous" sensitivity; it serves as an aid in preventing generalized eruptions prior to penicillin therapy and as a guide to dosage for desensitization. When the need for penicillin is urgent and a therapeutic desensitization is necessary, a provocative dose of from 1,000 to 5,000 units of penicillin might be given every three hours in the same dose for the first 24 hours, and the dosage increased each day following.

(Peck, Samuel M. New York N. Y. Siegel Sheppard, Clegg Arthur W., and Kurtin Abner. "Clinical Problems in Penicillin Sensitivity." *Journal of the American Medical Association* 138: 631-640 October 30, 1948.)

CHLOROMYCETIN

A new strain of *Streptomyces* named Chloromycetin, was isolated from a soil sample collected in a mulched field near Caracas, Venezuela, by Burkholder of Yale University. Cultures of this organism were found to inhibit adjacent inoculums of a wide variety of gram-positive and gram-negative micro-organisms. The crystalline form inhibits bacteria when tested in dilutions as high as 0.35 microgram per cubic centimeter, a higher effective dilution than that of the earlier antibiotics. More detailed studies of the therapeutic effects of Chloromycetin were undertaken by M. D. Smadel² and E. B. Jackson of the Army Medical Center, Washington, D. C.

Seven-day embryonated eggs infected with several rickettsial organisms were treated with Chloromycetin. Doses as large as 1 mg. per egg would reduce the mortality by at least 65 per cent. Sixteen of 24 treated eggs survived to the 15th day after infection and eight hatched normally. Similar therapeutic effects were noted in mice infected with scrub typhus. Daily intraperitoneal injections of as little as 0.1 mg. per mouse reduced the mortality by 62.5 percent, while 1.5 mg. doses reduced the mortality to zero. By doubling the dosage chloromycetin was equally effective if given orally.

Smadel and his associates suggest that chloromycetin might be of value in human medicine on account of its apparently low toxicity, ready absorption of chloromycetin from the alimentary tract and its beneficial effects when given relatively late in experimental disease. As a preliminary to a proposed study of its therapeutic value, Smadel and his associates administered single or repeated oral doses to a group of physician volunteers. After a single dose of 2 mg. appreciable amounts of the drug were demonstrable within 80 minutes in both blood and urine. The titers decreased to zero by the end of eight hours.

From this rapid elimination of the drug frequent oral administration is indicated in order to maintain the antibiotic at an appreciable level in the blood stream. With a 1 gm. initial dose followed by 0.2 gm. doses every four hours, the antibiotic can be maintained at an effective

level in the blood. Approximately 10 percent of the total amount thus given was recovered in active form from the urine. Toxic effects were not observed by the volunteer physicians during or after such administration. After this preliminary work on normal volunteers a group of five patients with typhus were treated with the same oral doses.³ In all cases there was a rapid fall in pulse rate and body temperature. The delirium and rash disappeared within three to five days and toxic reactions were not noted. Comparison was made with an equal number of patients with typhus not treated with the new antibiotic.

On the basis of these limited comparisons Smadel and his associates concluded that the administration of chloromycetin to patients with typhus is a safe procedure and that the therapeutic effects are sufficiently encouraging to warrant further tests of the drug with rickettsial and virus diseases. More extensive tests of this drug were made by the Malaya Institute of Medical Research, during the recent outbreak of scrub typhus at Kuala Lumpur.⁴ Twenty-five hospitalized patients were treated with chloromycetin, while 12 untreated hospitalized patients served as controls.

Treatment was begun on an average 6.2 days after the onset of the infection. All treated patients became afebrile within an average of 30 hours after the initial dose. The untreated patients remained febrile for an average of 18 days. Rickettsemia disappeared within 24 hours after the initial dose, and the rash within 48 hours. All treated patients were discharged from the hospital on an average of 13 days after beginning the treatment. The untreated controls remained on an average for 30.7 days after onset. No complications or deaths were noted with the 25 treated patients. Among the 12 untreated controls, in two, complications developed (parotitis, pneumonia), and one died.

(¹"Chloromycetin" Editorial, *Journal the American Medical Association* 138: 482-483 October 9, 1948)

²Smadel, J. E., Army Medical Center Washington, D. C., and Jackson, E. B. *Science* 106: 418, 1947.

³Smadel, J. E., Leon, A. P., Ley, H. L., and Varela, G. *Proc Soc Exper Biol and Med* 68: 12, 1948.

⁴Smadel, J. F., Woodward, T. E., Ley, H. L., Jr., Phillips, C. B., Trnub, R., Lewthwaite, R., and Savoor, S. R. *Science* 108: 160, 1948.

ACUTE LARYNGOTRACHEOBRONCHITIS

Although many articles describing the treatment of laryngotracheobronchitis have appeared in the literature, there is lack of agreement regarding the best methods of treatment. Because this fact is coupled with a high mortality—70 percent ten years ago and slightly lower today—F. W. Davison analyzes his own methods of treatment which resulted in no deaths in a series of 52 consecutive cases, 15 of whom required tracheotomy. All of the patients in this series had a dry, croupy cough, inspiratory stridor, retraction of soft tissues around the clavicles during inspiration and dyspnea. A clear cry indicated that the edges of the vocal cords were normal and free from membrane. Diphtheria and supraglottic edematous laryngitis were ruled out by laryngoscopic examination.

The author believes that dry indoor air in winter is one of the major predisposing factors in this condition, because it dehydrates mucous membranes, stops ciliary activity and thus permits organisms to penetrate the mucosa and set up inflammation. The patients were

placed immediately in a humidified oxygen tent, and the last 24 of the series were given penicillin, 15,000 to 25,000 units, by intramuscular injection, every two hours, day and night. The author states that acute laryngotracheo-bronchitis usually begins as a primary subglottic laryngitis due to any of the pathogenic gram-positive cocci which cause other types of infection of the respiratory tract. Because most of these organisms are sensitive to the action of penicillin, and because a lower percentage of penicillin-treated patients required tracheotomy as compared with sulfadiazine-treated patients, penicillin was considered the superior drug in this series.

The author concludes that the low mortality rate in this series is attributed to cool, moist air provided by a humidified oxygen tent; adequate doses of penicillin or sulfadiazine, preferably the former; avoidance of instrumental trauma to the mucosa of the trachea and bronchi by introducing the bronchoscope or the aspirating tube no farther than one inch beyond the vocal cords; postural drainage which avoids the retention of exudate which causes pneumonia; early tracheotomy; transfusion when indicated; and careful personal attention to each patient, including special day and night nurses before and after tracheotomy.

(Davison, F. W. Danville, Penn. 'Acute Laryngotracheobronchitis: Further Studies on Treatment' *Arch. Otolaryng.* 47: 255-264 April 1948)

PHEOCHROMOCYTOMA OF THE ADRENAL MEDULLA

Spatt and Grayzel present a study of several clinical types of pheochromocytoma and correlate clinical and pathologic findings where this is possible. A series of five cases, stated to be one of the largest groups reported from a single institution at any one time, are presented and are divided into three different types: (1) malignant adrenal pheochromocytoma with metastases; (2) benign adrenal pheochromocytoma with hypertension (paroxysmal or sustained); and (3) benign adrenal pheochromocytoma found incidentally at autopsy with no clinical signs or symptoms.

Of the cases presented, three are males and two females, ages ranging from 30 to 61 years. Case 1 was diagnosed as malignant bilateral adrenal pheochromocytoma with metastases to the brain. This patient's blood pressure readings were somewhat elevated during her hospital stay, which was explained by increased intracranial pressure with accompanying hypertension and slow pulse. The authors point out that hypertension is generally absent in malignant pheochromocytoma, and that this fact has not been explained. They think it probable that many of the malignant cells do not have the property of secreting the pressor substance as do the cells of the benign tumor. Cases 2 and 3 were benign tumors with paroxysmal and sustained hypertension, respectively.

The authors state that the benign pheochromocytoma with paroxysmal hypertension is well recognized. However, in the group with sustained hypertension, great room for improvement in diagnosis exists. In these latter cases the diagnosis must always be kept in mind and definite effort made to rule it in or out. The use of the Roth-Kvale histamine test or the benzodioxane test of Goldenberg

et al may be important in this respect. In cases 3, 4 and 5 a benign tumor with no signs or symptoms was found accidentally at autopsy.

According to the authors, the benign pheochromocytomas without clinical signs and symptoms have little or no diagnostic significance at present. However, the presence of hypertension in some patients with benign tumors and its absence in other with the same lesion is unexplained. There was some indication that these symptomless lesions were not precursors of the symptomatic ones from the comparative ages of the patients studied here. Finally, the authors note that the presence of symptoms does not seem to depend on the size of the lesion.

(Spatt S. D. Brooklyn N. Y. and Grayzel, D. M. "Pheochromocytoma of the Adrenal Medulla. A Clinicopathological Study of Five Cases." American Journal of Medical Science 216: 39-50 July, 1948.)

Reflections and Aphorisms

"The greatest *tyranny* has the smallest beginnings. From precedents overlooked, from grievances treated with ridicule, from powerless men oppressed with impunity, and overbearing men tolerated with complacency, springs the tyrannical usage which generation of wise and good men may hereafter lament and in vain.

At present, common minds no more see a crushing injury in a trivial unfairness or a ludicrous indignity than the cyc, uninformed by reason, can discern the oak in the acorn. Hence the necessity of denouncing with unwearied and even troublesome perseverance a single act of oppression."

THE TIMES, London, over 100 years ago

"*Courage* is not the absence of *fear*, it is the mastery of it."

"4 Hs"

"My HEAD to clearer thinking,
My HEART to greater loyalty,
My HANDS to larger service,
My HEALTH to better living"

"What is a *minority*? The chosen heroes of this earth have been in a minority. There is not a social, political, or religious privilege that you enjoy to-day that was not bought for you by the blood and tears and patient suffering of the minority. It is the minority that have stood in the van of every moral conflict, and achieved all that is noble in the history of the world."

JOHN B. GOUGH



The Indian Physician

VOL VIII NO 4

APRIL 1949

WHOLE NO 88

Original Contributions

ATRIAL SEPTAL DEFECT

WITH A REPORT OF TWO CASES *

by

V V SHAH, M D, M R C P (Lond.), M R C P E

T N Medical College and Nair Hospital, BOMBAY

Slit patency of the foramen ovale (to probe or even to pencil) is a commonplace finding in a normal atrial septum. It is present in 20-30 per cent of all necropsies and is clinically silent. As it should close during the first year of life, the patent foramen ovale is scarcely to be regarded as a congenital cardiac lesion, but rather as an anatomical variation of a pre-existent condition. In exceptional circumstances, an increase in the right atrial pressure can open up the slit foramen and determine or accentuate a terminal cyanosis. Pulmonary infarction may similarly enlarge the slit foramen and so facilitate the passage of a paradoxical embolus. Terminal cyanosis and paradoxical embolism are the only two events referable to this common condition and they are rare.

In contrast, an auricular septal defect (A S D) is a malformation that is really congenital and is embryologically and pathologically different from the foramen ovale, though both are characterised by an aperture in the auricular septum. It is the most frequent of all congenital cardiac malformations. As a single lesion it constitutes 7-25 per cent of all such cases. It is often associated with other congenital lesions like patent ductus arteriosus, ventricular septal defect, pulmonary stenosis and transposition of the arterial trunks, most often along with ventricular septal defect, with patent ductus arteriosus or with both. It may be complicated by complex lesions e.g. Fallot's tetralogy or multiple congenital defects or may accompany almost any congenital lesions.

In atrial septal defect, there is marked increase in size of the right auricle, right ventricle and pulmonary arteries. This is due to the extra blood, often in large amount, which enters the right auricle from the left auricle, through the septal defect. This direction of flow has been assumed to be due to a higher pressure in the left auricle but Uhley (1942) has shown that an important, perhaps the most important, cause of this direction of flow is the effect of gravity, the right auricle being anatomically situated below the left, the septum lying more or less horizontally. Precise diagnosis during life of congenital heart lesions

* Presented at the Staff Society Meeting of the B Y L Nair Charitable Hospital and T N Medical College, Bombay

has now more than an academic interest. Ligation of ductus arteriosus is a well established method of treatment, while the procedure of Blalock and Taussing in Fallot's tetralogy seems very promising. Cases of A S D reported in India are rare. Karmally (1942) reported two cases of atrial septal defect and Tulpule (1942) reported one case of Lutembacher's syndrome. Patel (1944) reported one case of A S D under the heading of Pulmonary Hypertension. On the other hand, Bedford, Papp and Parkinson (1941) reported 53 cases, 10 with necropsy control, Roesler (1934) has reviewed sixty-two cases of interatrial defect. Recently I came across two patients at B Y L Nair Hospital, Bombay, who were diagnosed as having atrial septal defect based on clinical, radiological and electrocardiographic findings. My purpose in reporting these cases is to emphasise the clinical and radiological features, as this congenital malformation is not often diagnosed. It is possible to make this diagnosis with little difficulty as one makes a diagnosis of other congenital defects like ventricular septal defect, Fallot's tetralogy, patent ductus arteriosus, Eisenmenger's complex, coarctation of the aorta, or pulmonary stenosis.

Case 1. Reg No 2244. Male aged fifty was referred to me by a surgeon as the radiologist, on routine screening of chest, reported aneurysmal dilatation of the pulmonary artery. There were no dyspnoea, cyanosis or clubbing of the fingers or other cardiac symptoms. The apex beat was seen in the left 5th intercostal space, mid-clavicular line and was not heaving. A faint systolic thrill was felt at the pulmonary area. A loud and harsh systolic murmur was heard best at the pulmonary area, the same murmur being heard all over precordium in lesser intensity, though very faint at aortic area. Pulmonary 2nd sound was markedly accentuated. Diastolic murmur, soft and blowing was heard at III and IV left intercostal spaces near the sternal margin. Signs of pulmonary congestion were absent and there were no signs of right-sided failure. Pulse rate was normal, rhythm regular, and B P S/D 124/80 mm Hg. The Kahn reaction of the blood was negative.

Radiological findings—In the anterior view (Fig 1) the heart is enlarged. There is a bulge in left upper silhouette—aneurysmal dilatation of the pulmonary arc, with an evenly rounded contour. The right branch is seen as a large dense, well-defined and comma-shaped shadow (B). On fluoroscopy, pulmonary artery, right branch as well as branches of left branch, were seen markedly pulsating, producing the 'hilar dance'. Lung fields were relatively clear. Prominent aortic knob in figure 1 is partly due to the tilted position of the patient.

Right-oblique position—Enlarged pulmonary conus and artery (Fig 2) is seen as increasing the width of the heart shadow in the upper third forming a squarish mass that bulges both to the front and to the back. An oval pulsating denser shadow could be discerned within it corresponding to the bifurcation and the right branch of the pulmonary artery seen in cross section. The posterior border in its lower position (left auricular) is straight, as very well shown in a barium filled oesophagus (Fig 3), quite unlike that seen in mitral stenosis.

The left-oblique position—(Fig 4) The left branch of the pulmonary artery hidden behind the greatly dilated pulmonary trunk in the anterior view, is seen partly encroaching upon the aortic window by appearing

under the aortic arch as a large denser shadow. Left ventricle is not enlarged and the sternal border of the heart is very prominent—enlargement of right ventricle.

Electrocardiogram —(Fig 5) There is right axis deviation in standard bipolar leads. Unipolar precordial leads -V1 shows inversion of T Wave and V2 and V3 show ST depression with biphasic T waves. Late or delayed intrinsic deflection and tall R waves in leads on right of

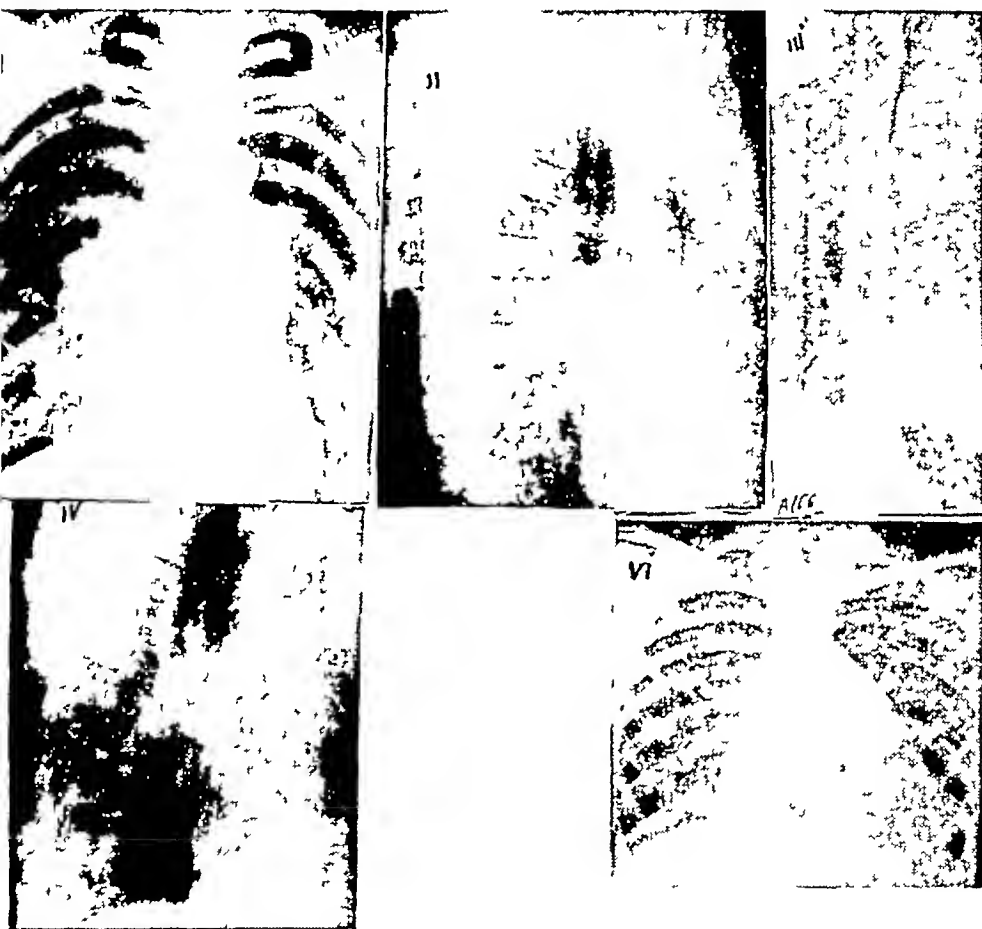


Fig —1, 2, 3, 4 and 6

precordium (V1, V2 and V3) indicate right ventricular hypertrophy. Prolonged intraventricular conduction, prominent S1, notched QRS complexes and precordial leads on the right side (V1, V2, V3) showing rsR'—pattern with inverted or biphasic T waves—all could be explained by right ventricular hypertrophy. This may be a transitional stage before developing into right bundle branch block with intraventricular conduction 0.12 second or more wide. It may be pointed out here that a widened ventricular complex, sometimes suggesting right bundle branch-

block in A S D was described by Bedford and Brown (1937), Router and de Balsac (1938) and its diagnostic importance was stressed by Routier et al (1940), this being not a part of the congenital lesion but a sequel to the progressive effect of the lesion on the myocardium, accompanied by enlargement of the right ventricle

Comments Absence of cyanosis and clubbing, good capacity for exertion, absence of pulmonary congestion, systolic thrill and murmur at



Fig —5

pulmonary area, 2nd pulmonary sound markedly accentuated, presence of a diastolic murmur (Graham Steell murmur—functional pulmonary regurgitation)—raised a strong suspicion of atrial septal defect in absence of any other obvious cause to explain these signs of dilatation of pulmonary artery, pulmonary hypertension and right ventricular hypertrophy. The great enlargement of pulmonary artery with its grossly dilated and pulsating right branch, associated with enlargement of right ventricle and absence of enlargement of left auricle and left

ventricle decided the diagnosis. Electrocardiogram gives positive evidence of right ventricular hypertrophy. The age of this patient is not against this diagnosis as Firket reported the case of a woman who died at the age of 74 years after having had 11 pregnancies.

Case 2 —Reg No 1041. A boy, fifteen years old, was admitted for joint pains and fever. There was a history of a similar episode one year back. There was no clubbing or cyanosis. He had fair capacity for exertion. Apex beat was in the left fifth interspace, $1\frac{1}{2}$ " away from mid-sternal line and was quite forcible. Diastolic shock and systolic thrill were felt at pulmonary area, and the latter was felt to a lesser degree more extensively. A loud and harsh systolic murmur was heard all over precordium, but well heard both at pulmonary area and at mitral area. Protodiastolic triple rhythm was heard in lower part of precordium. Diastolic murmur was heard at pulmonary area and a little lower down, 2nd pulmonary sound was markedly accentuated. First sound at mitral area was not short and sharp and mid-diastolic or presystolic murmur was not heard at mitral area. Signs of right sided failure with raised venous pressure and with an enlarged and tender liver were present on admission but disappeared later on. Pulse rhythm was regular and B.P. was S/D 90/60 mm Hg.

Radioscopy —(Fig 6). The heart is enlarged with a bulge at the left upper border. Pulmonary artery, right branch and branches of left branch are enlarged and were seen pulsating well. Right branch is seen as a comma shaped shadow. Aortic knob is absent. In oblique views, the right ventricle and pulmonary conus were seen markedly enlarged and the left pulmonary artery was seen as obscuring the aortic window. There was no or very little enlargement of left auricle on barium swallow. Lung fields were clear. ECG: Right axis deviation, (precordial leads not taken).

Comments —Configuration of heart with history of rheumatic fever would suggest mitral valvular disease, but absence of mid-diastolic or pre-systolic murmur, fair capacity for exertion in spite of the marked enlargement of heart, absence of pulmonary congestion and absence or very little enlargement of left auricle relative to the size of the heart led me to think of some other condition to explain these signs. This configuration might be explained by marked enlargement of pulmonary artery and pulmonary conus. History of rheumatic fever in this case is significant. The frequency of rheumatic heart lesions in cases of A.S.D. is in sharp contrast with the rarity of subacute bacterial endocarditis though this is very common with other congenital heart lesions. Roesler (1934), believes that 75% of the cases studied by him had rheumatic valvular disease. Among the 20 cases recorded by Rokitsky 11 had mitral stenosis and as also the four cases of Taussing et al (1938). In the series of 10 cases reported by Bedford, Papp and Parkinson with necropsy, mitral stenosis was associated in 4 cases. It will be evident, therefore, that A.S.D. is the only congenital lesion that occurs commonly with mitral stenosis (Lutembacher's syndrome). In view of rheumatic fever in the past, this patient may develop later on mitral stenosis.

Enlargement of heart and forcible apex beat will suggest left ventricular enlargement but the doubt was dispelled by radiological

examination in different oblique positions which showed marked right ventricular enlargement. Displaced and forcible apex beat is here produced by the enlarged right ventricle which pushes the left backwards and itself enlarges towards the left to form the apex beat. As Roesler (1984) maintains, "the displaced and often forcible apex beat so widely accepted as an index of left ventricular enlargement must be regarded an important sign of A S D in the absence of aortic valvular disease or hypertension."

The systolic thrill and murmur over the pulmonary area can be readily explained by the dilatation of both conus and pulmonary artery. The tricuspid orifice is so often enlarged that it may account for the loud systolic murmur which was well heard at the apex in this patient—the apex here being formed by the right ventricle.

Differential Diagnosis —The outstanding feature of A S D is great enlargement of pulmonary artery and its branches and, therefore, one has to differentiate this condition from those conditions congenital or acquired in which this is found *viz* mitral stenosis, patent ductus arteriosus, pulmonary stenosis, ventricular septal defect (Roger's disease), Eisenmenger's complex, pulmonary heart disease (cor pulmonale from emphysema), pulmonary artery disease and primary pulmonary hypertension.

In Mitral Stenosis typical mid-diastolic or pre-systolic murmur and invariable enlargement of left auricle, displacing the barium-filled oesophagus, are always present. Absence of pulmonary congestion and fair capacity for exertion in a patient with enlarged heart should make one revise the diagnosis of mitral valvular disease. In an advanced case of mitral stenosis with exceptionally large pulmonary artery with relative pulmonary incompetence (Graham Steell's murmur), it may give difficulties in diagnosis, but here, too, the enlarged left auricle and the diffuse pulmonary congestion, will exclude A S D whether with or without mitral stenosis. **In Ventricular septal defect**, gross enlargement of pulmonary artery is exceptional and the situation of murmur and thrill is typical. **In Eisenmenger's complex**, there are cyanosis, finger clubbing and dextroposition of aorta. A S D is common, Eisenmenger's complex is rare. **In Pulmonary Stenosis**, 2nd pulmonary sound is diminished in intensity or absent and the branches of the pulmonary artery are not enlarged, though the stem of the pulmonary artery may be moderately enlarged. **In Pulmonary Heart Disease**, enlargement of pulmonary artery is small and the cause like Emphysema, chronic bronchitis or fibrosis of lung is evident. **Pulmonary Artery Disease** is rare. The long history of pulmonary symptoms, erythraemia, cyanosis and positive W R will help in deciding the diagnosis. **Primary Pulmonary Hypertension** is very rare. One case, with necropsy control, was recorded by Howarth, McMichael and Sharpey Schafer (1947). In any doubtful case of gross enlargement of the pulmonary artery and its branches, A S D is the most probable diagnosis as this is so common while primary pulmonary hypertension is very rare. In deciding the shunt from left auricle to right auricle in A S D, cardiac catheterisation is useful. Samples of blood from the right auricle and superior vena cava are obtained and oxygen unsaturation estimated. Blood obtained from right auricle contains more oxygen than vena caval blood. It will also show a conspicuous increase in right auricular pressure.

SUMMARY

Two cases of auricular septal defect are reported. Essential diagnostic features have been emphasised. Differential diagnosis has been discussed. The paucity of cases reported in India is pointed out.

My thanks are due to Dr. C. H. Nerurkar, Honorary Radiologist, B. Y. L. Nair Hospital, for his help and to the Superintendent, B. Y. L. Nair Hospital, for permission to publish these cases.

REFERENCES

- BEDFORD D. E., PARR C. and PARKINSON J. (1941) *Brit. Heart Jour.* 3, 37.
- BEDFORD D. E. and BROWN J. W. (1937) *Brit. Encycl. Med. Pract.* Vol. 6.
- LINKET C. (1880) *Ann. Soc. Med. Chir. Liège* 19, 188 (Quoted by Roesler 1934).
- KARMALLY A. (1942) *Med. Bull.* 10, 42.
- PATEL N. D. (1944) *Indian Physician* 3, 9.
- PAUL DUDLEY WHITE (1940) *Heart Disease*, New York.
- ROESLER H. (1934) *Arch. Intern. Med.* 54, 339.
- ROESLER H. (1937) *Clinical Roentgenology of the Cardiovascular system*, London.
- ROUTIER D. and HEIM DE BALSAC R. (1938) *Bull. Soc. Belge Cardiol.* 5, 41.
- ROUTIER D., BRUMLIK J. and MALINSKY A. (1940) *Ibid.* 33, 40.
- SHEILA HOWARTH J., McMICHAEL and E. P. SHARPEY-SCHAFER (1947) *Brit. Heart Jour.* 9, 202.
- TAUSSINGO H. B., HARVY A. McC. and FOLLIS R. H. (1938) *Bull. Johns Hopkins Hosp.* 63, 61.
- TULPULÉ T. H. (1942) *Med. Bull.* 10, 48.
- UMLEY M. H. (1942) *Amer. Heart Jour.* 24, 315.

Clinical Case Reports

MALIGNANT HYPERTENSION, HYPERTHYROIDISM AND THYROTOXIC MYOPATHY (OR BULBAR PALSY) by N D PATEL and J M KAPADIA

B L, male aged 45, a Hindu goldsmith, sought medical advice on October 8, 1948, for (1) severe breathlessness which started about two months ago and was getting progressively worse, being present even at rest now, (2) dimness of vision for about four weeks, (3) palpitations off and on for about two months, (4) pain in the upper abdomen, and (5) swelling of the legs for about a month. The past history was essentially negative except for bloody stools from time to time during the last one year. There was no history of renal disease, venereal disease, or any period of sudden emotional disturbance. The family history and the personal history also did not show any significant facts.

Physical examination on admission showed the patient to be drowsy, though co-operative, in the fourth stage of congestive cardiac failure, with marked breathlessness at rest, engorged neck and arm veins, oedema of the legs, marked epigastric pulsation, enlarged and tender liver, and congested bases of the lungs. The cardiac impulse was heaving, and the apex beat in the left fifth intercostal space, 12 cm from the mid sternal line. The first heart sound at the apex and the second heart sound at the aortic cartilage were accentuated. There were no murmurs. The heart rate was 140 per min and regular in rhythm. The pulse gave a suggestion of collapsing type, and the blood pressure was 240 mm Hg systolic and 160 mm Hg diastolic. The spleen and the lymphatic glands were not palpable and there was no evidence of infection in the body. The face showed a myopathic appearance on the right side, with paralysis of the eye and the face muscles on the right side. There was no exophthalmos and no ocular

signs of Graves' disease. Pupils were equal, and reacted to light and accommodation. In the neck, there was a soft swelling in the centre, 10 cm x 5 cm in size, suggesting an uniformly enlarged thyroid gland. There was no thrill or murmur over it. There was frequency of stools, which contained frank blood. The reflexes were essentially normal. The *ophthalmoscopic examination* of the fundus showed a severe angioplastic retinitis of the grade IV of Keith and Wagener, with constricted arterioles, irregularities of the lumen (sclerosis), marked arteriovenous compression, oedematous disc and cotton wool patches, haemorrhages



and absorbing oedema exudate in the macular area producing a macular star

Laboratory Findings *Urine* examination showed the presence of albumen, pus cells, and granular hyaline casts but no red blood cells. *Stools* contained blood, but the microscopic examination did not show any evidence of dysentery either bacillary or amoebic. *Blood* Red blood cell count on admission was 4.2 mil per c mm and haemoglobin percentage was 80. The white blood cell count was 9750 cells per c mm with 64 per cent polymorphs, 1 per cent eosinophils, 82 per cent small lymphocytes, and 3 per cent monocytes. *Blood Chemistry* Urea nitrogen was 90 mg per 100 ml of blood on October 18, which rose to 150 mg per 100 ml of blood on October 19. *Cerebrospinal fluid* was not under tension, and was normal except for urea which was 160 mg per 100 cc of the fluid. *Basal Metabolism Rate* The patient was too low for estimation.

Progress Notes As cardiac failure was severe with marked dyspnoea which did not yield to intravenous aminophyllin, a venesection was performed and 300 ml of blood was removed which eased the patient a little. Because of tachycardia, goitre, and myopathic facies it was decided to put him on methyl-thiouracil, and a dose of 100 mgm three times a day was started on October 11. The blood pressure and the pulse rate began to fall and on October 15, they were recorded to be B P 160 mm Hg systolic and 100 mm Hg diastolic and the pulse rate of 96 per min and on October 19, they were B P 125/85 and the pulse rate 90 per minute. The blood urea had risen to 150 mg per 100 ml of blood but the patient's general condition had remained the same, drowsy, diarrhoeic and uraemic. He remained in the same condition till he expired on October 21. Unfortunately a post-mortem examination was not allowed.

Comments *Malignant Hypertension* is the term used by Keith, Wagener and Kernohan to describe a clinical condition occurring in young persons, under the age of forty, with a very high blood pressure about 240/160, and with a characteristic retinal picture where papilloedema is an essential feature. The clinical course is rapidly fatal, (two years or less, usually a few months only), ending in uraemia. The post mortem examination always shows *necrotizing arteriolitis* in the kidneys, with consequent widespread obliteration of glomeruli, accounting for the rapid onset of renal failure. Clinically the condition is to be differentiated from glomerulonephritis, and the swelling of the disks produced by intracranial tumours.

Malignant hypertension is nothing but a severe form of essential hypertension, which may arise quite suddenly, in younger subject, or engraft itself at any time on the benign form. The arteriolar changes are widespread throughout the body, affecting all the vital organs, and best seen in the fundus. The typical necrotizing arteriolitis in the kidneys is the result of severe arteriolar vasospasm.

Acute thyrotoxic bulbar palsy is a very rare condition, occurring in thyrotoxicosis. It is a rapidly spreading condition and always fatal within one or two weeks of onset. Paralysis may be relieved by prompt injection of prostigmine, which suggests its resemblance to myasthenia gravis.

Critical Notes and Abstracts

DIAGNOSIS AND TREATMENT OF MYASTHENIA GRAVIS*

by HENRY R. VIETS, BOSTON, (*Post-graduate Medicine, July 4 55-61*)

Myasthenia gravis is a somewhat rare disease not quite so rare as it was thought ten years ago, but still a disease of which there are probably not more than 1,500 cases in U.S.A. The death rate is now reduced from roughly 50 to 75 per cent down to less than 10 per cent. It is doubtful whether there are any more cases in the United States today than there were 10 or 15 years ago, but a lot more have been discovered than formerly. That is the very point of this paper, it is intended to show how such cases can be discovered and adequately treated.

The presenting symptoms of the disease vary a good deal. There is always a fatigue of voluntary muscles, but early in the course of this disease certain muscles are more easily fatigued than others. The muscles that have to do with movements of the eyes and eyelids are most frequently affected. In a little over 45 per cent of the cases the first symptoms often are ptosis and diplopia. If you have this disease in mind—which unfortunately many physicians do not—you will consider seriously the possibility of myasthenia gravis when you have a patient with a sudden ptosis and double vision without obvious cause, the symptoms fluctuating during the day or during the week or month, and usually being better in the morning after a night's rest and worse in the afternoon.

The second group is even more important because they have no distinctive and outstanding muscle signs. The patients come in on account of general weakness, fatigue in walking upstairs, difficulty in raising their arms and doing ordinary household tasks. This is the large group, about 30 per cent of the total, that have general muscular weakness and is confused most often with cases of neurasthenia.

Another group, comprising about a 5th of the cases, have dysphagia, and dysarthria. Here again there is a fluctuation in symptom—the patient may have no trouble in swallowing breakfast but will have difficulty with luncheon and increasing trouble with supper. Speech is affected the same way—after a few minutes the voice becomes nasal, and always on rest there is a tendency to restoration of function to normal. That is the key of the whole disease.

There is still another group in which neck weakness is an important feature and is sometimes the only symptom. A patient will notice suddenly one morning on washing his face in the bowl that he will start to lift up his head and he will be unable to do so. If he rests a few minutes he can lift his head normally.

Thus the ophthalmologist may see the ptosis and diplopia cases, the laryngologist may see the dysphagias and dysarthrias, the general weakness group usually falls to the general practitioner, as does the group affected only with neck weakness, but any of them may be seen by anyone at any time.

Let us look at the age group, which is another important point. They spread all the way from the very earliest years of life to well into

* (Myasthenia Gravis is not very rare in India. The Editor has seen three cases in Bombay during the last one year — Ed 1 P)

the 80's, and interestingly enough there is a large group of patients between 60 and 70 which we had never discovered before. One should look at the older age group as a very important and formerly undiagnosed group of patients with this disease.

Neostigmine (Prostigmine-Roché) is a diagnostic as well as a therapeutic agent for the disease. It is the only drug that has any marked effect upon myasthenia gravis. There are others that have some effect but this is the drug that has the most marked effect and the one that is used as a diagnostic test. As a diagnostic test, the dosage is 1.5 mg. of neostigmine methylsulfate given subcutaneously. The methylsulfate is the soluble form put in an ampule, and to that is added some atropine to overcome the intestinal stimulation which often goes along with the initial use of the drug. There is a diagnostic ampule now available containing the proper dose for an adult and the proper amount of atropine in one ampule.

Neostigmine is found to be an almost specific remedy in the diagnosis and treatment of this disease. It overcomes in large part the one principal symptom, namely, muscular weakness, and because of that we use it as a diagnostic agent. If a patient has ptosis, diplopia, facial weakness, difficulty in chewing, difficulty in talking, or difficulty in swallowing, and the drug is injected subcutaneously in the appropriate amount as given in the diagnostic ampule, the patient will, in about 20 to 30 minutes, recover entirely, or in very large part, all use of the affected muscle. It is perhaps one of the most dramatic changes that we see in all medicine. No other disease responds in this remarkable way. Other diseases may give a slight response, but certainly under 10 per cent, whereas the response in myasthenia gravis runs up to 85, 90, or even 100 per cent as in this picture. Therefore, the diagnosis is clinched if this response is present.

Neostigmine is used in two ways. In the diagnostic test it is always used subcutaneously. In the treatment of patients it may be used either subcutaneously or orally. All our patients take the medicine orally in the form of prostigmine bromide, the only tablet made for oral medication. There are 10 mg. of neostigmine bromide in each tablet. The average intake in my clinic is 15 to 12 a day. If that amount is given and if the lateralization of the dose is correct throughout the day, a patient ought to be practically free from symptoms at all times. One does not reach that height always, but that is the aim to balance the neostigmine against the symptoms of the disease and to make the patient as well as possible.

Neostigmine treatment turns out to be a form of substitution therapy. Something has dropped out of the body, there is a chemical dysfunction at the junction of the nerve and the muscle, neostigmine is added to this myoneural junction or synapse and the chemical reaction is restored to normal, or partially so. One must think of this as a form of substitution therapy exactly as one thinks of insulin in diabetes or liver therapy in pernicious anemia.

That point is a very important one, because the minute you grasp it your whole attitude toward this disease becomes a life problem. Success can be reached only if the patient is continually under the doctor's care or observation, presumably for the rest of his life. Be sure, he may have long periods of remission in which he

Apart from elimination of the cause of the disease, which is not possible at this time except in rare instances, it would appear that the main object of treatment should be to retard or prevent development of vascular disease which is the ultimate cause of disability and death. No significant progress has been made in this direction.

It is our present considered opinion that any treatment directed solely toward temporary reduction of blood pressure is futile. Final treatment will come only when the causative mechanism of human hypertension is discovered and specific measures are devised for its elimination.

Except for the rare instance of pheochromocytoma of the adrenal and the very rare instance of unilateral renal disease, hypertension is not curable. Present methods of treatment are merely designed to alter the clinical aspect of hypertensive disease either by eliminating subjective symptoms or by lowering blood pressure. When both can be accomplished, patient and doctor are lulled into a sense of security but whether or not any of the measures of treatment now at hand actually retard the progress of hypertensive disease is extremely doubtful. In spite of this pessimistic attitude toward present-day treatment for hypertension and with full knowledge of what it means to the worried patient and the equally worried doctor, it would appear to be a healthier attitude and more likely to lead to ultimate solution than an attitude of ready acceptance which has the potentiality of engendering a false sense of security.

DEFICIENCIES IN PREGNANCY *By* WINSLOW T. TOMPKINS, M.D.,
(*Bulletin of the New York Academy of Medicine*, June 24 376-388)

In 1935 the author undertook to evaluate by clinical observations, the effect of improved nutrition on maternal and infant well-being. The initial efforts were directed toward establishing a minimum optimum diet for pregnancy, one which would, of course provide an adequate caloric value, estimated on the basis of the patient's weight at the beginning of pregnancy and her energy requirements. But of greater importance, one which would supply necessary amounts of animal and non-animal protein, carbohydrates and fats, and at least minimal protective amounts of the known vitamins and minerals. Since the average weight at the beginning of pregnancy, among the patients registered in the Prenatal Clinic was found to be 129 pounds, their standardized diet was arbitrarily established on this weight basis. It contained approximately 2,200 calories, consisting of 110 Gm. of protein (of which approximately 80 Gm. being animal protein), 85 Gm. of fat and approximately 300 Gm. of carbohydrates.

The success which the author has had with improved nutrition in his research group of patients has been dependent upon several factors, among which are: The patients attending the Research Clinic have been given intensive and persistent dietary instructions, both written and oral. It should be emphasized that this is primarily the physician's responsibility, and that only by individual dietary analysis, investigation of the patient's dietary habits and the specific correction of the dietary errors noted, can adequate results be obtained. The simple expedient of giving the patient a printed dietary outline, or telling her to eat a "well-balanced" diet, is ridiculous on the face of it.

Six small meals a day, at approximately three-hour intervals, have been found to be essential, and the author has found a marked improvement will result in all patients if this regime of interval feeding is adhered to. Such a regime has been found to decrease markedly the severity of nausea and vomiting during early pregnancy, and to aid in the elimination of fatigue and other symptoms associated with energy depletion. The gastro-intestinal tract becomes hypotonic surprisingly early in pregnancy, and unless adequate measures are instituted immediately, this dysfunction will continue or become exaggerated and will result in a failure of intestinal absorption with resulting maternal and fetal shortages.

Fruit and Fruit Juices—Total fluid intake is limited to eight glasses a day. Except where excessive salt intake is demonstrated, the restriction of salt has been found unnecessary. The author's instructions to patients to refrain from eating pastry, ice-cream, candy and nuts, have been questioned as being a ridiculous request to make of any woman during pregnancy. In working with large groups of patients certain standards must be established, and it has been found that the above advice is essential, and except in isolated cases, has not produced any hardship or lack of co-operation on the part of his patients once the reason for this restriction is understood. The caloric requirements during pregnancy can not be arbitrarily stated for all patients. As stated above, we have established our specific dietary instructions on the basis of a beginning pregnancy weight of 129 pounds which we have found to be average. Obviously, patients weighing 90 pounds or 175 pounds at the beginning of pregnancy will require an entirely different caloric intake to maintain optimum gain in weight during their pregnancy. To answer the necessary energy requirements, diets containing 1600 calories or less which have appeared in the literature from time to time, cannot possibly supply optimum or essential nutrients, and diets containing 3,000 or more calories are in excess of the caloric requirements for the average patients.

The simple expedient of handing the patient a printed dietary outline is of no value in a long range nutritional programme. Few, if any, patients understand the real reason for nutritional reinforcements during pregnancy, and they are entitled to complete and detailed individualized dietary instructions from their doctor.

Vitamin Deficiencies—Although nutritional deficiency of an advanced degree is comparatively uncommon in the Philadelphia area, sub-clinical states are by no means infrequent. The incidence of *glossitis* is 98 per cent of our patients and *polyneuritis* in at least 54 per cent clearly indicates the frequency of deficiency states of minor degree. The author observed an incidence of sub-clinical *scurvy* in approximately 82 per cent of his patients. The *gingivitis* so commonly seen in pregnancy is usually attributed to an infection. It is true that infection is frequently present, but generally the underlying cause of the disturbance is a lack of Vitamin C.

The author's observations show a much greater incidence of *Vitamin A deficiency* than has heretofore been suggested. Straumfjord states that *verruca caseosa* is a manifestation of deficiency of Vitamin A. This, together with other reported evidences, points to the

fact that a high percentage of patients are lacking in adequate amounts of this factor

The necessity for adequate amounts of the Vitamin B-complex for satisfactory metabolism of protein and carbohydrates is well established, and the majority of the clinical observations of deficiency are characterized by evidence of a lack of these important vitamins

Pregnancy demonstrates more readily than almost any other condition the fact that adequate intake of food in no way guarantees optimum absorption, utilization or storage, yet it must be emphasized that it is essential to obtain the necessary nutritional elements from natural food sources, rather than from supplemental therapy alone

The importance of vitamin supplementation became more and more apparent as his clinical experience progressed, and further, such experience indicated that this supplementation should consist of a relatively high potency polyvitamin concentrate. Many workers have stated that the requirements for such factors as thiamin chloride, riboflavin, niacin and ascorbic acid are relatively low. The author's observations clearly indicate that during pregnancy, the requirements for the known vitamins are comparatively high. This is especially true of the vitamin B-complex factors.

Throughout this study it has been observed that in many cases, a typical syndrome developed during the middle or latter part of the second trimester. This syndrome is characterized by fatigue, lassitude, mild depression and general physiologic hypotonia. Frequently, this has appeared in patients known to be co-operating with the author's nutrition advice. With the advent of parenteral B-complex, patients of this type have made a prompt and satisfactory response to therapy, where previously they responded poorly if at all. This strongly suggests that even these apparently well stabilized individuals may fail adequately to absorb or utilize a well planned and optimum diet. It further demonstrates that in many cases there is an absolute necessity for parenteral polyvitamin supplementation, in order to by-pass the oral route, to re-establish normal intestinal absorption and efficiency. The indication is that the primary breakdown responsible for the development of disturbances occurring in the pregnancy, is usually initiated by an absorptive failure in the gastro-intestinal tract, rather than a utilization failure. It should be emphasized that in pregnancy, parenteral vitamin therapy is essential in acute deficiency states, and may be necessary even in the mild chronic types in order to obtain a satisfactory nutritional balance throughout the remainder of pregnancy.

The author did not use supplemental calcium therapy in the research group of patients, and does not believe that calcium in its present available supplemental form is of any value in the prevention of dental caries, or as a substitute for calcium from natural food sources.

Anaemias of pregnancy—The author believes that supplemental iron therapy alone is of little value, and that iron deficiency anaemias occurring in pregnancy are rare. Most of the anaemias being typically nutritional anaemias, do not respond to iron alone unless accompanied by an adequate diet and supplemented with vitamin and whole liver therapy. Recent observations suggest a more prompt and marked response when iron was omitted and whole desiccated liver substituted,

It is well established that hypoproteinemias are a major factor in the production of hydremia. Since secondary, or simple, anemias of pregnancy are usually stated to be the result of a physiologic hydremia, it is his opinion that the high incidence of the secondary anemias of pregnancy is the result of hypoproteinemias, and the associated general under-nutrition. He does not believe that the so-called physiologic hydremia of pregnancy is normal, but is in fact evidence of hypoproteinemias, and will increase as the intake of protein decreases, or requirements for protein increase. Therefore, his efforts are directed early in pregnancy toward a primary improvement in the patient's basic dietary, rather than the useless administration of iron, or hematopoietic stimulants without consideration of essential nutritional requirements.

Torremas of pregnancy—It is of considerable interest that in most patients with pre-eclampsia, the condition is readily reversible by means of nutritional therapy alone. This is particularly true if the onset of pre-eclampsia is recognized early and adequate nutritional therapy is immediately instituted. The author believes that the rate of gain in weight is the most important early clinical observation relative to the onset of pre-eclampsia. Patients adhering properly to his nutritional instructions, and maintaining a positive nutritional balance, have been found to maintain a weight curve characterized by either a plus or minus three pounds the first trimester. Whether this is a plus or minus, ascending or descending curve, will be determined by the amount of severity of nausea and vomiting which occurs. The weight curve should rise one-half pound per week the second trimester, and one pound per week the third trimester, up to about the 37th or 38th week, at which time the weight usually remains constant, or slightly decreases.

During the second trimester, it is of critical significance if a patient gains two or three times as much as she should. For example, during the second trimester, the patient should gain two pounds per month, whereas many patients and doctors would attach little significance to a gain of four pounds during this period. However, this four pounds represents twice as much as the patient should have gained, and if this rate of gain is continued into the third trimester, no one would disagree that the patient's weight gain was in definite excess of optimum. Intensive efforts at nutritional stabilization should be instituted at any time during pregnancy that the gain in weight is excessive. Pre-eclampsia which has been allowed to continue even in a mild form, for a considerable period, will be found difficult to improve, and may even be irreversible. This strongly suggests a physiologic breakdown in the patient's metabolic process beyond a point commensurate with the comparative slowness of nutritional therapy instituted late in pregnancy. This further indicates the absolute necessity for early nutritional stabilization as a preventive measure, rather than waiting until after a catastrophe has occurred and then relying on emergency measures.

PROTEIN-ITS IMPORTANCE IN NUTRITION OF PREGNANCY by CLARENCE H. BOSO, M.D., (*West Virginia Medical Journal*, August, 44 213-217)

A pregnant woman differs from other women in her pro-
To the basic need of the non-pregnant woman are added

of an increased metabolism, the storage of nitrogen, growth of the woman's body, increased needs for fetal growth and repair, growth of mammary tissue and the hormonal preparation for lactation. If 1 Gm of protein per kg of body weight per day is accepted as the ordinary adult need, then—particularly during the latter half of pregnancy the amount should be increased to $1\frac{1}{2}$ Gm. The Food and Nutrition Board of the National Research Council suggests a daily intake of 85 Gm for the normal pregnant woman and 100 Gm for the lactating woman.

Protein is obtained by an individual from food. Unfortunately only a few foods, are sources of good protein. The nutritional quality of any food is dependent on its content of amino acids, particularly those which are essential. Generally speaking, proteins of animal origin are of higher nutritional value than the commonly used vegetable proteins, since the former contain all the essential amino acids. Vegetable proteins contain many of the essential amino acids, however, and in properly selected diets may supplement one another, resulting in adequate protein ingestion. It is thought that about 66 per cent of the pregnant woman's protein intake should be of animal origin. The remainder is supplied by vegetables, nuts and legumes, and from bread and cereals.

One of the main things that has been noted by many observers is the relative infrequency of the development of the specific toxemias of pregnancy in patients who receive optimum amounts of protein in their diets. It is not generally thought, however, that hypoproteinemia is the cause of toxemia, or that the amount of edema in toxemia can in any way be co-related with plasma protein levels. The facts now prove that it is illogical to restrict protein intake in the treatment of the toxemia of pregnancy.

Anemias are frequent during pregnancy. Probably many of these anemias are caused by nutritional deficiencies. It is reasonable in the treatment of such an anemia to administer iron and also to increase the intake of animal protein.

In the presence of high protein intake, 15 per cent of ingested calcium is absorbed, as compared with only 5 per cent in cases of low protein intake. This probably means that amino acids facilitate calcium absorption. This relationship should be a significant one in pregnancy.

To insure that the patient will have an adequate supply of breast milk, preparations must be made during pregnancy. An adequate intake of varied proteins is essential to provide for the growth of the breast, and to permit it to withdraw sufficient amino acids for synthesis of the particular protein which is characteristic of the mammary secretory elements. The specific protein the hormonal action of which is necessary for continued production of milk, is also synthesized from amino acids.

Patients who take diets adequate in protein exhibit an increased sense of well-being, less tendency toward constipation, less weight gain with less tendency to retain this weight, after delivery, and an increased resistance to intercurrent infection. They are also found to have shorter and more normal labors.

Infants born to mothers receiving less than 75 Gm of protein daily in the latter part of pregnancy tend to be shorter and lighter, and to

receive a lower pediatric rating. A strong relationship is found, on X-ray examination, between protein intake and osseous development of the baby.

There can be no doubt that an increased intake of protein is essential for the well-being of the expectant mother and of her unborn baby. Just as she is instructed in the hygiene of pregnancy, so should she be individually instructed in the quantity and quality of food she should eat. The result will be a healthier child, and a mother more capable of caring properly for him.

EVALUATION AND MANAGEMENT OF THE CARDIAC PATIENT FOR ANESTHESIA AND SURGERY by F. F. ROSENBAUM, M. D. (*Wisconsin Medical Journal*, October, 47: 989-998)

Surgical procedures in patients with heart disease call for close co-operation of the physician, anesthesiologist and surgeon, in order that the potential hazards may be evaluated and anticipated. The risk of anesthesia and surgical treatment in patients with heart disease can be reduced by appropriate management to a level only slightly greater than that in patients with normal hearts.

There have been several clinical and experimental observations reported recently which bear importantly upon the greater risk and mortality of surgical treatment in patients with coronary arterial disease. Blumgart has found that shock no matter how produced, may lead to multiple, as well as single, fresh coronary arterial occlusions in elderly patients with coronary arteriosclerosis. In Masters' cases of post-operative myocardial infarction, the incidence of shock was high. Furthermore, the coronary arterial flow in dogs is decreased by 80 to 60 per cent during periods of hypotension due to hemorrhage. Patients who have been operated upon may be able to distinguish cardiac pain from the various discomforts attendant upon the surgical procedure. Consequently, myocardial infarction occurring during the immediate postoperative period may be overlooked.

The implication of these various observations is clear. In order to reduce the risk of surgical treatment in patients with coronary arterial disease, the following recommendations seem wise: (a) The operation should be delayed until the cardiac disorder has become stabilized. It is now recognized that patients whose cardiac pain is changing—that is, becoming more severe, more frequent, or occurring on lesser stress—may be having premonitory manifestations of myocardial infarction or may already actually have had an infarct. Surgical procedures should be postponed until the pain has become stable in its character. Electrocardiographic observations may be especially helpful in patients of this type. If there has been a recent myocardial infarction, the operation must wait until cardiac lesion heals completely. This usually requires 3 to 4 months. Of course, it is true that delay may be impossible in dealing with acute surgical emergencies. (b) Shock and especially prolonged hypotension should be avoided. (c) If shock or dehydration should occur, the complication must be treated promptly and adequately. Transfusion appears to be the most certain means of preventing cardiac damage in shock. Parenteral fluids and blood must be given cautiously, however, to avoid overloading the circulation by suddenly increasing the total circulating blood volume. The sympathetic

be used carefully, if at all, lest angina pectoris or prolonged coronary arterial spasm be produced

Patients who have cardiac disorders associated with congestive heart failure or potential cardiac decompensation present problems of a somewhat different character. The usual program for management of congestive heart failure must be employed to get these patients into the best possible condition prior to operation. Mild ambulation prior to operation is a better preparation for these patients than strict confinement to bed, but too much exertion may cause a recurrence of heart failure. Digitalis should be given preoperatively only if the usual indications of congestive failure or auricular fibrillation exist. It should not be given to "tone up the heart" or merely because heart disease is known to be present. If the need for digitalis arises postoperatively, cardiac glycosides such as digoxin or strophanthin can be given parenterally for rapid effect.

There are a few precautions which seem indicated in the postoperative management of patients with actual or potential cardiac decompensation. If parenteral fluids or blood are given, they must be administered slowly and in cautious amounts to prevent sudden increases in the circulating blood volume and recipitation of acute pulmonary edema which may be fatal. The rate of administration probably should not exceed 300 cc per hour. Fluids containing sodium must be avoided if the patient has had congestive failure, and they are probably unwise in all cardiac patients in time of stress. Oxygen should be used freely postoperatively if there is any suggestion of circulatory embarrassment, and in some cases it may be beneficial preoperatively. If acute pulmonary edema does develop, in addition to the more usual measures, venous tourniquets on all four extremities may reduce the circulating blood volume by as much as 1 liter. Large, wide blood pressure cuffs maintained at just above the diastolic level are more satisfactory for this purpose than most tourniquets. Oxygen administered under positive pressure may be helpful in preventing further exudation of fluid into the lungs. If the patient does not improve promptly, one should not hesitate to resort to venesection, with removal of 500 to 1,000 cc of blood. The greater hazard of pulmonary embolism in patients with heart disease, especially those with increased venous pressure and congestive heart failure, is an added reason for early postoperative ambulation in cases of this type.

Individuals who are subject to paroxysms of significant cardiac arrhythmia may be prepared for operation by prophylactic preoperative medication. Quinidine is usually effective in preventing paroxysmal supraventricular or ventricular tachycardia, as well as paroxysmal auricular fibrillation or flutter. It may be given in doses of 0.2 Gm (3 grs) for 2 or 3 doses at hourly intervals immediately prior to the operation. Digitalis is more effective than quinidine in occasional instances, and in such cases it is usually well to digitalize the patient completely in the usual fashion. It is usually wise to avoid those anesthetic agents such as cyclopropane and chloroform, which tend to produce cardiac irregularities, when dealing with cases of this type.

VITAMIN B₁₂ IN COMBINED SYSTEM DISEASE by LIONEL BERK, M D, DERE DENNY-BROWN, M D, MAXWELL FINLAND, M D and WILLIAM B CASTLE, M D, Boston, (*New England Journal of Medicine*, August 26, 1949 328-330)

A crystalline substance, vitamin B₁₂, has recently been isolated from liver extracts and found to produce hematologic remissions in pernicious anemia. An unusual opportunity for testing the effectiveness of vitamin B₁₂ upon the neurologic disturbance of pernicious anemia, presented itself in patient who had developed acute combined system disease while receiving hemopoietically inadequate doses of synthetic pteroylglutamic acid. The patient also had an acquired allergic sensitivity to injected liver extracts. It was of additional interest, therefore, to determine the relation of vitamin B₁₂ to this sensitivity.

Case Report—A 41-year-old mulatto woman entered the hospital on May 26, 1948, because of ataxia. She had been admitted to the hospital because of anemia, 6, 4 and 2 years previously. Histamine-fast achlorhydria was demonstrated repeatedly, and at the first two admissions she showed adequate hematologic and clinical response to the injection of purified liver extracts. After she had received injections of liver extracts derived from pork for 9 months without discomfort, she experienced generalized urticaria and itching after each of two such injections. Relief followed a change of therapy to bee-liver extract. After receiving the latter for 10 months the patient began to react to this substance also. Positive skin tests to both pork and beef extracts were demonstrated, nine different commercial liver preparations being used. Consequently, on the third admission in September 1946, she was treated intramuscularly with synthetic pteroylglutamic acid (folic acid) in doses of 10 mg daily for 10 days, again with typical hematologic and clinical responses. No neurologic changes were demonstrable at any of the three admissions.

Before discharge from the hospital she received 4 doses of folic acid, 75 mg each intramuscularly at intervals of a week. After discharge she attended irregularly for injections, and hence received an average of one each month for the next year. Because of failure to reach normal blood values she was started on 50 mg of folic acid orally daily on September 9, 1947, and she continued to take this amount until the end of the year. At about Christmas time she developed some numbness and stiffness of the hands, together with difficulty in their use for finer motions. This lasted 4 or 5 weeks and then disappeared completely. From this time she took folic acid irregularly, sometimes averaging one dose of 50 mg every other day, but at other times omitting therapy for periods up to 1 week when her supply of medicine ran out.

Apart from some throbbing in the upper part of the chest she felt well until 1 week before entering the hospital. At that time, while walking in the street, she suddenly experienced a sensation of pressure about the abdomen as if she were wearing an elastic girdle, and at the same time her gait became unsteady. These symptoms persisted with some fluctuation in severity. Her legs felt numb from the knees down, and she had to be helped to the hospital by two friends because of the difficulty in walking.

Physical examination showed a pale, well nourished woman with normal findings except on neurologic examination, which reveal gross ataxia with positive Romberg's sign and defective position sense and pinprick perception in the toes. There was absence of vibratory sensation in the lower extremities. The planter responses were of flexor type. The day after entering the hospital she noticed numbness of the tips of the index and middle fingers, and examination demonstrated hypalgesia at these sites.

Examination of the blood disclosed a red-cell count of 1,920,000 with a hemoglobin of 6.5 Gm per 100 cc (42%), a mean corpuscular volume of 104 cubic microns, a mean corpuscular hemoglobin concentration of 32% and a mean corpuscular hemoglobin of 38 micromicromgm. The reticulocytes were 0.6%, and the white-cell count was 2200.

The patient was placed on diet free of meat, fish and eggs. Folic acid was discontinued, and no antianemic therapy was given for the first 4 days. On the 4th hospital day she was grossly ataxic in walking, requiring continued support and assistance.

On the 5th hospital day treatment was started with injections of vitamin B₁₂ (supplied by Merck & Co.) in doses of 5 microgm daily for a total of 8 injections, the first being given intradermally, and the subsequent ones intramuscularly. The intradermal injection was given in 0.2 cc of physiologic saline solution, producing a wheal that reached a maximum size of 2 cm in 30 minutes and subsided entirely in a few hours. No systemic symptoms followed the intradermal or the subsequent intramuscular injections of vitamin B₁₂, each of which contained 5 microgm, an amount approximately 45 times as great as that contained in the 0.01 cc of liver extract tested.

The reticulocytes began to rise on the 4th day of treatment and reached a peak of 16.0% on the 6th day. By this time the patient felt well and displayed an excellent appetite. After 10 days of vitamin B₁₂ therapy the red cell count and the hemoglobin had risen to 2,840,000 and 9.0 Gm per 100 cc (58%), respectively.

Remarkable changes in the neurologic disorder were already evident by the 10th day of treatment. The recent numbness of the fingers and clumsiness in using them had vanished by the 4th day. On and after the 6th day of treatment an extensor plantar response was rarely obtained. By the 10th day the patient could walk without support, with only occasional unsteadiness, the tendon reflexes were of normal amplitude, and the plantar responses were both clearly flexor. By the 13th day mild vibration was appreciated in the right patella, and maximum vibration was perceived in the right tibia and left patella.

Beginning on the 9th day after the start of therapy, treatment with vitamin B₁₂ was discontinued for 7 days because of delay in obtaining a further supply of the material. After the 13th day there was a slight setback in the neurologic improvement, so that by the 19th day, there was a reversion of neurologic signs to their status of the 6th and 10th days. This finding was reported by the neurologist without his knowledge of the lapse in treatment.

Treatment was reinstituted on the 16th day in doses of 5 microgm of vitamin B₁₂ intramuscularly 3 times a week. By the 21st day further improvement was already appreciable. Sixty days after the beginning

of treatment, the patient's gait was natural and she was able to stand with eyes closed without swaying. There was still slight numbness of the right great toe, but no elsewhere. The plantar responses were both clearly flexor, the tendon jerks were of normal amplitude, and there was doubtful, if any, disorder of sensation to touch or pinprick. Sense of position was acute in all extremities. Vibration was just appreciated over the internal malleolus on the right side and was readily perceived over both tibiae and patellas.

These findings, indicate that, as with previous stages in the purification of liver extract, the achievement of a crystalline derivative with intense hemopoietic activity has not diminished the ability of the material to arrest and in part to reverse recent neurologic manifestations of pernicious anemia. The dramatic changes in this patient strongly suggest that a deficiency of vitamin B₁₂ is closely related to the natural origin of both the blood and the nervous changes. They should not be interpreted to mean that vitamin B₁₂ was more effective than treatment with liver extract would have been.

It is evident that the neurologic lesion in this patient was in great part reversible, exemplifying the stage of "biochemical lesion" that precedes the structural degeneration of the spinal cord. The experience recorded above emphasizes the well-known fact that spinal cord symptoms of combined system disease constitute a medical emergency. The longer the lesion has existed, the more difficult it is to reverse.

The findings in this case also suggest that allergic sensitivity to liver extract is due not to sensitivity to the active principle itself but to other material in liver extracts, with species specificity, as demonstrated by Bauer and his co-workers.

Book Reviews and Notices

YEAR BOOK OF PEDIATRICS-1948, Edited by Henry G. Poncher, M.D. (pp. 542 + 4 50) The Year Book Publishing Co., Chicago

Pediatrics has now for quite some time established itself as a special subject in medicine requiring adequate study and attention for the proper care of the young patients. Treatment of the ailing child is no longer a matter of merely calculating the appropriate dose, by one of the many accepted formulae, as a fraction of the adult dose. The ailing child is a problem in itself and requires a special study of its diseases, its peculiar response to drugs, its individual reactions to the various problems of growth, feeding, immunization, infection and other physiological and pathological processes. The year book of pediatrics serves the useful purpose of bringing home to the busy general practitioner recent views about these problems and their solutions. As its new editor Dr. Poncher, who incidentally takes up the onerous task from Dr. Isaac Abbot, says, the book primarily deals with practical aspects of pediatrics particularly diagnosis and treatment for the help of the family physician who is responsible for 75 per cent of the care of children. However, in catering for the general practitioner the interests of the specialist are not completely ignored and there are many articles on

The Indian Physician, April 1949

recent technical developments in subjects like congenital heart disease, cardio-angiography, and surgical treatment of cardiac anomalies. The chapter on tuberculosis deals at length on the revived use of BCG as an immunization agent and the place of streptomycin in the treatment of tuberculosis. The chapter on therapeutics and toxicology is perhaps the most interesting one from the point of view of one who has very little time to spare and wants the maximum information in a minimum of time — All told this is a very useful book for the specialist as well as the general practitioner and Dr Poncher is to be congratulated on the excellent way in which he has selected his material from an ever increasing literature.

YEAR BOOK OF ENDOCRINOLOGY METABOLISM AND NUTRITION 1947
 Edited by Willard O. Thomson M.D. and Tom D. Spies M.D. (pp 575 + 3 75). The Year Book Publishing Co Chicago M D M

The second volume of this addition to the year book series lives up to the high standard set up last year. Dr Thompson editing the section on endocrinology allots quite a good deal of the available space to the adrenals, testes and ovaries. Though intended to serve the specialist as well as the general practitioner the matter is generally of the type that would be useful to the clinician in his day to day work. The immense strides taken by the rapidly progressing science of endocrinology and its great contribution to the chemotherapeutic armamentarium of the clinician make it absolutely essential for a physician to have some basic knowledge of this branch of medicine, and keep in touch with the recent advances in it. Over and above the use of hormones, natural and synthetic, in various endocrine disorders, recently a new and a very wide vista has been opened out by the partial success achieved by this group of drugs in the treatment of hitherto unassailable malignant diseases. It is too early to say whether the services of the surgeon and the radiologist would ever be completely dispensed with, as far as the treatment of malignant diseases is concerned but it may be said now, without the charge of uncritical overenthusiasm, that the recent trends in the chemotherapy of the malignant diseases with the hormones hold out some hope of making the life of a victim of this disease comfortable where the surgeon and the radiologist are helpless. This has been fairly well brought out in several papers abstracted in this volume. There are quite a few papers included which deal with the various animal experiments in the field of endocrinology and they help the inquiring student in the better understanding of the many complex problems of endocrinology. The section on metabolism and nutrition is in the very capable hands of Dr. Tom Spies and includes a fairly large number of papers on the perennially recurring problems of diabetes mellitus, relapses in pernicious anemia, various aspects of cirrhosis of the liver, tropical and non-tropical sprue syndrome, and malnutrition. In this section there are critical abstracts of many papers of an experimental and technical nature which will be of interest to the research worker.

THE INTERNATIONAL JOURNAL OF SEXOLOGY, Vol II no 3 February 1949.
 Edited by Dr A. P. Pillay OBE MBBS (Quarterly, subscription Rs 12, Sh 22, \$ 5 50), Hornby Road, Bombay, I M D M

This issue of the journal contains many interesting articles on the problems of sex in its various aspects. The article on the Ethics of Sexual Acts by Dr Harry Benjamin is very thought-provoking and may

seem almost as revolutionary as the writings of Dr Rene Guyon, which it tries to defend, if that celebrated author is in any need of defence. The other articles cater to varied tastes and on the whole the journal provides interesting and instructive reading, maintaining a balanced view on matters of sex. We hope the editor is sending complimentary copies to the Home Department of the Government of Bombay Province, and to the Chief of the Police, if they are not regular subscribers. M D M

Opinions and Diversions

When anything is asked of a physician he usually starts with—"In my opinion," and makes a statement which his next door colleague is only too willing to contradict or agree with many a reservation. Now what are *opinions*? The Oxford Pocket Dictionary, an infallible guide in the proper use of words, tells us that an opinion is 'belief based on grounds short of proof, a view held as probable'. A belief is an acceptance of something as true. When you know a thing is true you don't say 'I believe', you say 'I know'. What can be known should not be believed, *i.e.*, merely accepted as true, it should be affirmed. If somebody asked of me, 'Is so and so in the house?' and if I knew for certain, I would answer 'Yes, go in the library and you will find him'. If I was doubtful I would answer, 'I believe that he is in'. This will help the inquirer little, for he may go in every room in the house looking for the individual and come back without finding him and still my answer was correct. Opinions and beliefs are probabilities, not certainties, and still it is best to have them, when there is no definite knowledge. A man with opinions is better (if he has an open mind and is willing to change his opinions as new facts arise) than a man without any opinions, right or wrong.

Diversions are reliefs from work or absorption, amusement or pastime. Perhaps the best definition of diversion is that of Halifax from his *Advice to a Daughter* (1700). "*Diversions are most properly applied to ease and relieve those who are oppressed by being too much employed*"

These columns will contain opinions on a variety of subjects, medical or otherwise, and something by way of diversions for busy practitioners absorbed in their special activities to relieve the monotony of their labour. They should be read for what they are worth, thoughts of a physician or free flights of imagination, perhaps rash, perhaps wise, but always intended to stimulate and to divert.

Death thy Neighbour

"*Lastly, if Length of Days be thy Portion, make it not thy Expectation. Reckon not upon long Life, but live always beyond thy Account. He that so often surviveth his Expectation lives many lives, and hardly complain of the Shortness of his Days. Time past is gone like a Shadow, make Times to come, present. Conceive that near which may be far off, approximate thy last Times by present Apprehensions of them. Live like a Neighbour*

unto Death, and think that there is but little to come And since there is something in us that must still live on, join both Lives together, unite them in thy Thoughts and Actions, and live in one but for the other He who thus ordereth the Purposes of this Life will never be far from next, and is in some manner already in it, by an happy Conformity, and close Apprehension of it" Sir Thomas Browne, *A Letter to a Friend*, 1690

The problem of Death is often prominent in the mind of a medical practitioner He always tries to fight it in his patients and sometimes, though not as often as he would like, he succeeds in putting it off, but often, alas too often, he meets with failure and with resignation accepts the inevitable When he realises this inevitable end and feels that he must tell his patient about it, it is wise for him to pause and reflect that it is only an opinion, he may be wrong, there is hope as long as there is life and many a man has lived for years after passing through most serious crises Does the patient want to know the truth, the near end? The experience of all physicians is that he rarely does, and to offer an unasked opinion is meddlesome unwarranted practice on the part of the physician, perhaps unconsciously motivated to satisfy some inner vain need or frustration No wise practitioner should ever fall an easy prey to it The relatives who clamour for truth, and who have their own theories based on preconceived notions, have to be satisfied, but then they should be told only the probabilities and not imparted all the fears and conjectures passing through the physician's mind Like Sahadev the 'विकालज्ञानी', no unasked question should be answered, unless it is in the interest of the patient, but when a definite question is asked the answer may not be evaded or shirked Truth as one knows it must be given, though it may be tampered with tact and mercy, Yudhishthir's 'नरो वा कुजरो वा' method of stating the truth is perfectly valid for a physician Most ill persons do not ask for the truth, they only ask for cure, relief, or reassurance The more serious the disease and the more hopeless the outlook, less the desire for truth, and less the clamour Usually the inevitable is accepted with quiet resignation and indifference

Death of Swami Vivekanand

It is always fascinating to know or guess about the death of eminent men How did they live their terminal days? For some of the great men of the world there are detailed records of their last illness and the mode of termination, for others there is nothing and one has only to fall back on conjectures During the last fifty years many eminent Indians have died from *Diabetes*—a common disease among us, poorly understood and most ineffectively treated G K Gokhale (1915), B G Tilak (1920), C R Das (1925) and many others have succumbed to it in comparatively young or early middle age Swami Vivekanand was also known to have diabetes mellitus and succumbed to it at an early age of thirty-nine after a volcanic life of energy and enthusiasm Vivekanand may well be claimed as the philosopher of the New Resurgent India who lighted the torch of freedom which Gandhiji carried on to its logical end We are not concerned with his religious, or mystical life People will always differ on these aspects of his life Swami Vivekanand (Narendra Nath Dutt, born January 12, 1863, died July 4, 1902) became Rama-

krishna's disciple in 1884 and after the death of Ramakrishna (August 15, 1886), became the head of the monastery Vivekananda had suffered from malaria in his youth and also from severe diphtheria in childhood. It was discovered during his journey to America and Europe that he was suffering from diabetes mellitus. In New York as early as 1895 he felt that his volcanic vitality was being gradually ebbing away and he actually said "*my day is done*". On August 23, 1896, age 33, he wrote "*I am getting ready to depart, to return no more to this hell, this world*". "The arrow of Vivekananda was finishing its trajectory." He returned to India in 1897 and founded the Ramakrishna Mission. In July 1898 he undertook the great pilgrimage to the cave of Amarnath. During this journey on foot he overstrained himself. He entered the cave, naked, smeared with ashes like others, quite exhausted almost in a fainting condition, and emerged from the cave with a blood clot in his eye and a dilated heart, from which he never recovered. In November 1898, he had attacks of asthma from which 'he emerged with his face blue like that of a drowning man'. With this state of myocardial failure, he made a second journey to the West and returned to India in December 1900 quite worn out, and despite the difficulties of a mountain journey he went to Mayavati Monastery in the Himalayas on January 3, 1901, carried by disciples amidst the falling snow, the mist and the clouds. This journey made his cardiac condition worse. At Mayavati he had asthma which suffocated him, the least physical effort exhausted him. "*My body is done for*". He knew the end was near, the journey of his life was ended. "*What does it matter? I have done enough for fifteen hundred years*". He celebrated his thirty-eighth birthday on January 13, 1901, left Mayavati on January 18, travelled for four days on slippery slopes, partly through the snow, and returned to his monastery on January 24, 1901, and remained there till the end except for a pilgrimage with his mother to holy places of Eastern Bengal, Assam and a short stay at Benares at the beginning of 1902. At Belur his illness progressed, he developed dropsy. The doctors restricted his water intake. For twenty-one days he did not swallow a drop of water, even when he rinsed out his mouth. "*The body is only the mask of the mind. What the mind dictates, the body will have to obey. Now I do not even think of water, I do not miss it at all*". A profound statement which may well be taken as a basis for the psycho-somatic concept of disease.

Of his last day, his biographer, Romain Rolland writes "On the supreme day, Friday, July 4, 1902, he was more vigorous and joyous than he had been for years. He rose very early. Going to the chapel, contrary to his wont of opening everything, he shut the windows and bolted the doors. There he meditated alone from eight to eleven o'clock in the morning, and sang a beautiful hymn to Kali. When he went out into the court he was transfigured. He ate his meal with an appetite in the midst of his disciples. Immediately afterwards he gave the novices a Sanskrit lesson for three hours and was full of life and humour. Then he walked with Premananda along Belur road for nearly two miles, he spoke of his plan of a Vedic College and talked of Vedic study. "*It will kill superstition*" he said.

"Evening came—he had a last affectionate interview with his monks and spoke of the rise and fall of nations. "*India is immortal*",

he said "*if she persists in her search for God But if she goes in for politics and social conflict she will die*"

"Seven o'clock The convent bell sounded for Aratī (worship) He went to his room and looked over the Ganges Then he sent away the novice who was with him, desiring that his meditation should be undisturbed Forty-five minutes later he called in the monk, had all the windows opened, lay down quietly on the floor *on his left side* and remained motionless He seemed to be meditating At the end of an hour he turned round, gave a deep sigh—there was silence for several seconds—his eyes were fixed in the middle of his eye-lids—a second deep sigh—and eternal silence fell

'There was' said a brother-disciple of the Swami, 'a little blood in his nostrils, about his mouth and in his eyes'

"It seemed he had gone away in a voluntary fit of Kundalini Shakti—in the final great ecstasy, which Ramakrishna had promised him only when his task was completed He was thirty-nine"

Whatever the disciples may say the end of Vivekananda was no voluntary act of yoga discarding an unwanted body The whole history as given above suggests the presence of *coronary disease in a diabetic subject*, who had perhaps *hypertension* He had strained his heart during his pilgrimage to the cave of Amarnath in the Western Himalayas Eversince that time he had attacks of "asthma" suggesting left ventricular failure If he had any precordial pain, there is no mention of it A great yogi, who thought his body to be under the control of his mind perhaps thought little of it, such a man would consider it a sign of weakness to talk about pain The description of the last day is also very suggestive of acute coronary occlusion The doctor who saw him the next day suggested apoplexy as the cause of death This is not likely Apoplexy rarely if ever kills suddenly like this Coronary thrombosis in a diabetic with hypertension fits in better with the facts Vivekanand's whole personality with his tempers, enthusiasms, repressions, violent emotional storms, and yogic exercises to control the unruly psyche, suggests a high blood pressure or coronary personality, as described by Flanders Dunbar In her own words, with our italics "Coronary cases have generally a distinguished appearance with considerable evidence of control Few classical neurotic traits are manifest but their typical life pattern of *asceticism* and *hard work* cloaks and rationalizes many compulsions They present a *surface calm* with little appearance of strain The tension, until a crisis arises, is mainly a smooth muscle tension In times of stress they tend to *brood and seek solitude* The coronary patients have a general air of *self sufficiency* and they tend to *dominate social relationships* through superior argumentative skill Accepting the idea of hierarchy they identify with *authority figures* and strive to become *super-authorities* The coronary accident in these patents is precipitated by an apparently irreparable mutilation of their picture of themselves through external threats to their authoritative role"

THE TECHNIQUE OF FREEZE-DRYING

A LITTLE KNOWN ASPECT OF PENICILLIN MANUFACTURE

After the 'brewing' of penicillin in the giant, throbbing stills there is one almost insignificant but now highly developed process which, but for its work, would render every single vial of penicillin in the world unstable and therefore useless. But for its existence Fleming's famous discovery might have been confined to the text book and the high hopes centred on the so far only lightly touched subject of antibiotics never raised. That process is freeze drying. Penicillin is like a prima donna for it is notoriously sensitive—it is unstable when first produced as a liquid and, once dried will absorb water and lose potency at the slightest opportunity. Freeze drying ensures it doesn't get that opportunity.

Freeze drying is the method by which the ice in previously frozen penicillin vials is placed under a high vacuum at a very low temperature and, without melting, undergoes vapourisation. Visualise a fragment of ice standing in a dish over a fire. Watch the ice melt to form water and then trace a further stage in its evolution as it reaches boiling point and is finally given off as water vapour in the form of steam to complete the cycle. In freeze drying science has liquidated that intermediate stage and we now see ice being transformed into vapour in one single operation. It is an example of science ruthlessly side-stepping one of the natural processes and therein lies its fascination.

In the early days of British penicillin manufacture, one of the two large scale penicillin producers in Great Britain, Glaxo Laboratories Ltd., of Greenford, began freeze drying their penicillin solutions in glass-ware apparatus. When the company came into the antibiotics field in 1943, at a time when the greatest possible output of penicillin for the forces was being called for, it was fortunate in being able to call on Dr R. I. N. Greaves, of the serum drying unit at Cambridge and other medical Research Council Scientists, to assist with the various problems of freeze drying.

It is indeed not an exaggeration to say that had it not been for that assistance from Dr Greaves and his colleagues—who had developed the technique of freeze drying from the experimental stage to successful large scale operation—the volume of output of penicillin from the Greenford factory would have been greatly reduced. Penicillin has to be freeze dried because of various chemical peculiarities in its make-up. The sodium and calcium salts which are isolated in the process of manufacture as a solution in water are unstable in that form and have to be converted to a dry solid as quickly as possible. Once dried the penicillin remains stable under normal conditions but since the drug has the irritating habit of quickly absorbing moisture whenever it has the chance the need for keeping it perfectly dry after freeze drying becomes of first rate importance, if it is not to lose any of its potency. Since the stability of liquid penicillin falls with any rise in temperature and the final dry substance has to be sterile, drying by either spray or roller drying is not considered advisable.

And so in the early days the freeze drying technique of using glass apparatus with "dry ice" as a refrigerant worked quite well although the quantity of penicillin which could be handled was necessarily small on account of limitations imposed by the size of the flasks. It then became the aim of the company to step up the number of glass units in service. At the peak period no fewer than eight banks or 80 flask units were in continuous use and gave the Glaxo concern the enviable reputation of having produced at least eighty per cent of the total British war time penicillin output.

There were great disadvantages in this method of freeze drying however. "Dry ice" was costly, running costs soared and there were frequent expensive breakages. Nor was that all. The dried product in those days came out of freeze-drying plant as dry powder. In pharmaceutical preparations this was convenient form but for the more highly needed injection purposes it had to be filled into bottles under aseptic conditions. To do so accurately was a most difficult operation.

As soon as the large scale deep culture method of penicillin production was introduced into Britain new freeze drying equipment, capable of handling the increased volume, became a paramount necessity. In collaboration with refrigeration experts the company's engineers set to work on new designs and before long permanent, up to date, and fundamentally different freeze-drying equipment was in

operation at Greenford. When at the end of the war Glaxo moved its penicillin production unit to a brand new factory at Barnard Castle in Co. Durham to begin large scale deep culture manufacture the new equipment went too and today the freeze-drying hall is one of the most impressive departments in the concern.

In an atmosphere of quiet efficiency the deep-freeze cabinets (in which the penicillin solution is originally frozen) a battery of glistening, white cylindrical drying chambers which freeze dry the penicillin and the high vacuum pumps which exhaust the air from these chambers are in operation 24 hours a day. At the control panel, at one end of the long room, white-coated technicians keep a careful watch on recording thermographs and other gauges. It is methodical, high precision work.

Most of the penicillin produced at Barnard Castle is freeze dried in the small vials which eventually go to the hospitals, doctors and chemists. The vials reach the freeze drying hall in containers after being semi automatically charged with penicillin and are then ready for the freezing cabinets. This process takes about five hours and at the end the containers are removed to the drying chambers by technicians wearing anti-frostbite clothing. Every chamber holds 21 containers and these in turn hold no fewer than 3,000 vials. The chamber is closed and sealed and air is exhausted by the high vacuum pumps. In the chamber a special condensing coil is kept at a temperature of 50 degrees centigrade and when the required vacuum is reached the ice begins to evaporate from the vials without melting and condenses on the coil. Since there is a tendency for the penicillin in the vials to cool still further—evaporation would cease when it reached the temperature of the coil—there is the somewhat ironic necessity to heat the vials. This problem is overcome by the installation of thermostatically controlled electric heaters which are mounted under each container.

In about five hours the complete drying cycle is completed and the result is a vial of perfectly dry penicillin ready for the final sealing process. At the Glaxo plant the maximum number of vials are put through the freeze-drying process with the minimum amount of handling and this consideration dominated the design and layout of the equipment. Additionally the work is performed with the minimum labour. Night and day the freeze-drying plant is in operation and provides one further link in the chain which aims at providing the maximum amount of penicillin for consumption in all parts of the world.

TWO NOTABLE CONTRIBUTIONS

STREPTOMYCIN

Glaxo Laboratories are already producing sufficient Streptomycin, in spite of many difficulties of production, to provide Britain with her present needs and that in the near future, it is expected the output will be considerably increased.

VIT. B₁₂

After years of research work Glaxo Laboratories have succeeded in isolating from liver the *anti-pernicious anaemia factor* in pure crystalline form, known as Vit. B₁₂. (It is made experimentally also by Merck & Co., Rahway, N.J., U.S.A.—*Ed. Ind. Phys.*)

For the present the discovery is regarded more as a scientific achievement than as a commercial possibility. The difficulty of the problem can be realised if it is appreciated that, from one ton of liver, only a few grains of the substance can be extracted—a few specks of ruby coloured dust sufficient to cover a four anna piece. The substance produces excellent results in amazingly small doses of 1/200,000 of an ounce.

Fortified with the knowledge of this new substance, it is expected that, in due course a further practical contribution will be made to the treatment of pernicious anaemia.

What does the discovery mean for those afflicted with pernicious anaemia? Already clinical tests have shown that not only are the red blood corpuscles restored but that the various neurological symptoms—nervous disorders and the deterioration of the spinal cord—are corrected by minute doses of the new substance. It will also mean that standardised doses of the extract will, for the first time, be capable of preparation, further it will be possible for massive doses to be administered without physical discomfort to the patient.

Original Contributions

KALA-AZAR AN ENDEMIC FOCUS IN BOMBAY

A PRELIMINARY COMMUNICATION

by
Y M BHENDE, M D N FIGUEREDO, M B B S B Hy
N M PURANDARE, M D S D DESAI, M B B S
D D BANKER, M D

(Acworth Leper Home Matunga, BOMBAY)

(Dept of Pathology & Bacteriology Gordhandas Sunderdas Medical College, Parel, BOMBAY)

Hitherto, Bombay has been considered a "dry" area for Kala-azar and the cases of Kala azar encountered locally have been classed as "imported", meaning thereby that the affected individuals caught the infection outside in some endemic zone, and migrated to Bombay subsequently. During the last two or three years a feeling has grown among the local practitioners that at least in some of the cases detected in Bombay the circumstances are such as to suggest an indigenous origin from a local source of infection. Though many more such cases may have been seen, only two have been reported so far. In the 1st case,¹ the patient was a resident of Bombay for 22 years, and during that time the only place, outside Bombay, he had visited was Poona (another "dry" area for Kala-azar, about 120 miles from Bombay). In the 2nd case² the patient had resided in Bombay for 18 years and the only place, outside Bombay, he had visited was Bassein (about 40 miles from Bombay). In both these cases the diagnosis was unequivocal. Leishmania donovani were demonstrated in smears of the sternal marrow and the leptomonas grown from the marrow or the peripheral blood. These reports, therefore, offer strong but circumstantial evidence for the possible existence of an endemic focus of Kala-azar in Bombay.

In this communication we submit positive proof for the above thesis.

1 *Outbreak of Kala-azar in a Local Institution* —Whenever possible all the bodies from the Acworth Leper Home are submitted for autopsy to the Department of Pathology and Bacteriology of the Gordhandas Sunderdas Medical College. From April 1948 to April 1949 autopsy was done on 18 such bodies. Of these, 9 patients were found to have suffered from Kala-azar (in addition to leprosy). In every case Leishmania donovani were unequivocally demonstrated in the smears and/or sections of the organs (mostly the liver and the spleen). Further investigations have shown that among the present inmates of the Home there are at least 8 more cases of Kala-azar, in these Leishmania

L. donovani have been demonstrated in smears of the sternal marrow and the leptomonas grown in cultures from the same material. A series of 12 cases in a single institution within a period of 1 year is by itself very suspicious of an indigenous origin. A critical analysis of the case-records of these patients revealed the following—Except 3 who came from Madras (a proved endemic focus for Kala-azar) and 1 who came from Goa (a suspected endemic focus), the rest have their native places in the Bombay Province which so far has been considered a non-endemic area for Kala-azar. The determination of the duration of their stay in Bombay proper from the total period of their segregation was misleading because many of them had absconded from the home on two or three occasions and their movements outside could not be verified. The period of definite stay in Bombay was, therefore, calculated in each case from the date of the last re-admission to the date on which death occurred or up to date in the case of patients still alive. The figures obtained for the 12 cases were—34 days, 71 days, 86 days, 125 days, 129 days, 5 months, 6½ months, 1 year, 1 year and 1 month, 3 years and 2 months, 3½ years, and, 13 years and 4 months. These figures, be it noted, indicate the *minimum* duration of these patients' stay in Bombay. The exact range of the incubation period of Kala-azar is not known but is assumed to be anything from 10 days to 2 years. That many of our patients could have caught the infection in Bombay is, therefore, probable and that at least 3 of them with a minimum of 3 years' un-interrupted stay in the Home were infected locally is almost certain. In our opinion these figures suggest very strongly that the whole outbreak is of local origin and not a chance accumulation of "imported" material.

2 *Presence of the Insect-Vector*—Controversy still rages round the possible insect-vectors for Kala-azar, but, the sand-fly is the only one for which irrefutable proof has been obtained. After trapping hundreds of flies and examining each of them carefully we have been able to establish the presence of phlebotomi in the wards of the Acworth Leper Home in which these cases of Kala-azar were discovered. The insect-vector proved responsible for the transmission of Kala-azar from one person to another is, therefore, present in the locality affected.

3 *Presence of Infected Sand-Flies*—With the exception of a few mounted as permanent specimens, every sand-fly was dissected and smears prepared from the material obtained by crushing the pharynx and the mid-gut. Up to date 3 female phlebotomi have shown the presence of leptomonas in the smears. A careful study of these forms has convinced us that morphologically they are the leptomonas of *L. donovani*.

A detailed report of these investigations is in preparation and will be published shortly.

REFERENCES

- 1 ROW, R. & PATKAR, N. A. *Indian Physician* 6: 251, 1947
- 2 RAGHAVAN, P. *Indian Physician* 6: 3, 1949

LIVER FUNCTION AND THE VITAMIN B—COMPLEX

A PRELIMINARY REPORT

by

E P BHARUCHA, M.D. Honorary Assistant Physician
R G CHITRE, M.Sc. Ph.D., A.M.C. Asst. Prof. of Biochemistry,
A F GOLWALLA, M.D. F.C.P.S. Medical Registrar
and
B Y NADKARNI, M.Sc., Technical Assistant

K F M Hospital Patel BOMBAY

Introduction

Despite the rapid advance that chemotherapy has made in other fields during the last 20 years, the prophylaxis and treatment of liver disease is still largely confined to the realms of dietetics.

The evolution of the present dietetic regime of hepatic disorders is an interesting one, extending over more than three decades.

In 1912, Opie and Alford on the basis of experimental work introduced high carbohydrate diet into clinical practice. Many years after this Ravidin and his associates noting the beneficial effects of a high protein intake on the liver parenchyma instituted a high carbohydrate, high protein regimen in the treatment of liver diseases. At a still later date supplements of yeast, liver extract, and vitamins were added to the now rapidly swelling list of "protective" substances. The newest addition to this imposing array are the "lipotropic agents" of the nature of choline and methionine. Thus came into being the present day dietetic scheme adopted in the treatment of liver damage connected with the names of Patek and others.

In this connection, it seemed of interest to us to find out whether any quantitative improvement could be demonstrated, by adding supplements of the vitamin B complex to the diet of individuals showing evidences of deficiency of this vitamin. In the present investigation subjects with obvious manifestations of vitamin B deficiency were selected and a series of liver function tests performed both before and after the administration of large doses of vitamin B complex. The liver function tests selected were those which as far as possible could be used as a quantitative expression of liver function. Supplements of vitamins A, C, D and proteins were given parenterally for some days prior to the investigation in order to prevent a deficiency of these from vitiating the results.

The patients selected for study, all showed gross manifestations of deficiency of one or more vitamins of the B complex and usually to a much smaller extent of other vitamins as well.

Procedure

The following procedure was adopted in the present investigation. Before admission Routine screening was performed to exclude

A Paper read before the 87th Meeting of the G.S. Medical College and K.E.M. Hospital Staff Society on November 18 1948

pulmonary tuberculosis in every case and patients with a hemoglobin per cent below 85 were excluded

On admission and first 5 days (1) A detailed history taking and clinical examination was performed with special emphasis on evidences of vitamin B complex deficiency

(2) Collection of the next 24 hours sample of urine (in a Winchester bottle with the addition of 20 c c of 5% acetic acid) was commenced. The urinary excretion of thiamine, riboflavin and niacin was determined in this sample of urine. Thiamine was estimated by Thiochrome method, Riboflavin by Pyridine butynol extraction method and Niacin by cynogen bromide and aniline hydrochloride method, the first two being fluorometric and the third a colorimetric method

(3) On the 2nd day an intramuscular injection of prepain (Glaxo) 60,000 units of vitamin A and 10,000 units of vitamin D and injection of 500 mgm of vitamin C were given. Subsequently each patient received the juice of 2 sour limes and 3 ounces of the hospital codliver oil mixture daily throughout his stay in hospital. In diarrhoeic cases parenteral vitamin A and D was given throughout

(4) Daily injections of casein Hydrolysate 50 c c of a 5% solution (25 gms) were given intravenously from the 2nd to the 5th day

(5) Diet The patient throughout his stay was kept on the standard hospital diet, containing—

	<i>Calories</i>	<i>Proteins</i>	<i>Fat</i>	<i>Carbohydrate</i>
Vegetarian	2252	80 Gms	78 Gms	290 Gms
Non vegetarian	2054	60 „	55 „	310 „

6th and 7th day The first series of liver function tests were performed. The Liver Function Tests employed were —

- 1 Thymol Turbidity test
- 2 Cephalin Cholesterol Flocculation test
- 3 Bilirubin Excretion test.
- 4 Bromsulphalein Clearance test
- 5 Serum Protein estimation and determination of the Albumin-Globulin ratio
- 6 Takata-Ara test

8th, 9th, 10th, 11th day (1) Patients were given intramuscular injections of vitamin B complex daily from the 8th day onwards, containing not less than 30 mgms Thiamine, 5 mgms Riboflavin and 75 mgms Niacin. In addition each patient received 12 yeast tablets (Thiamine 36 mgm, Riboflavin 18 mgm and Niacin 0.9 mgm) per day.

(2) On the 10th day *i.e.*, after 3 days of vitamin B complex the urinary excretion of Thiamine, Riboflavin and Niacin was again estimated to judge the amount of saturation of the body with these vitamins. If this showed adequate saturation with vitamins B complex, the second series of Liver Function Tests were performed. If there was not sufficient saturation, the estimation was repeated after increasing the dose of the vitamin B complex and it was only when saturation was attained that the investigation was proceeded with.

Results

In the present series 10 cases showed an increment of liver function after administration of vitamin B complex. The distribution of improvement in the various tests was as follows —

C C + T T + B S + Bilirubin	6 cases
T T + B S + Bilirubin	9 "
B S + Bilirubin	10 "
C C + A G ratio	5 "
C C + T T + A G ratio	4 "
C C alone	8 "
T T alone (Identical with Bil and B S)	9 "
Bilirubin alone	10 "
Bromsulphalein alone	10 "
A G ratio	9 "

C C = Cephalin Cholesterol test

B S = Bromsulphalein test

T T = Thymol turbidity test

A G = Alumbin Globulin

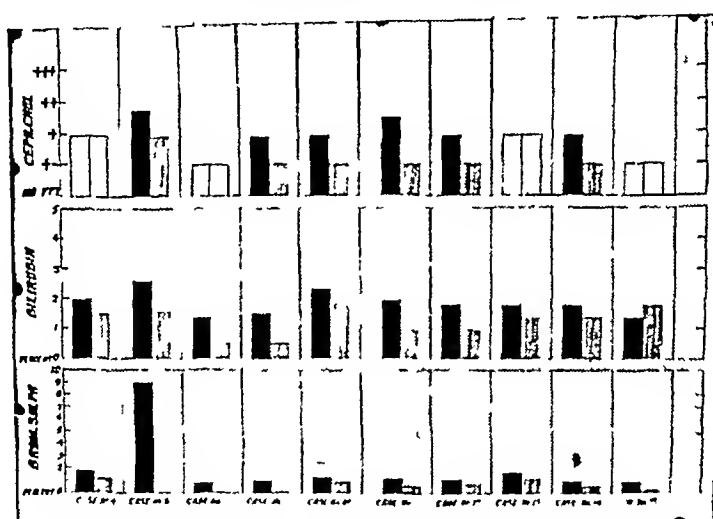


Chart I

The chart illustrates the liver function in the improved cases as well as the urinary excretion of Thiamine, Riboflavin and Niacin before and after administration of saturating doses of the vitamin B complex.

It will be seen from this that the values for urinary excretion of Niacin are high even before saturation with the vitamins. This is in keeping with the findings of others that the urinary excretion of Niacin is no index of saturation with this vitamin and that the urine of patients contains considerable amounts of this substance.

Discussion

Correlation of the Various Tests

An attempt will now be made to correlate and explain the varying results in the different liver function tests performed in the present investigation.

Takata-Ara Test

(1) Was hardly of any use in the present series, being unchanged in all except two cases in which it showed some improvement after administration of vitamin B complex.

Serum Proteins and Alb Glob Ratio

(2) The plasma protein level in the majority of cases was low (normal 6-8 gms per 100 c c) as also was the albumin content (normal 4-4.5 gms per 100 c c). The critical level for oedema has been shown to be a serum protein content of below 5.5 gms per 100 c c and an albumin content of 2.5 gms per 100 c c. In 5 cases (Case Nos 6, 9, 11, 13 and 14) where dropsy was present, the serum protein content was adequate. This is in keeping with the findings of Sinclair (1947) on extensive observations made in Holland and Germany in which the albumin and total protein concentrations were within the normal range in the serum from cases of famine oedema. The oedema may be due to lowered colloid osmotic pressure (Govaerts) or to decreased renal excretion of water and salts or to deficiency of vitamin B complex itself.

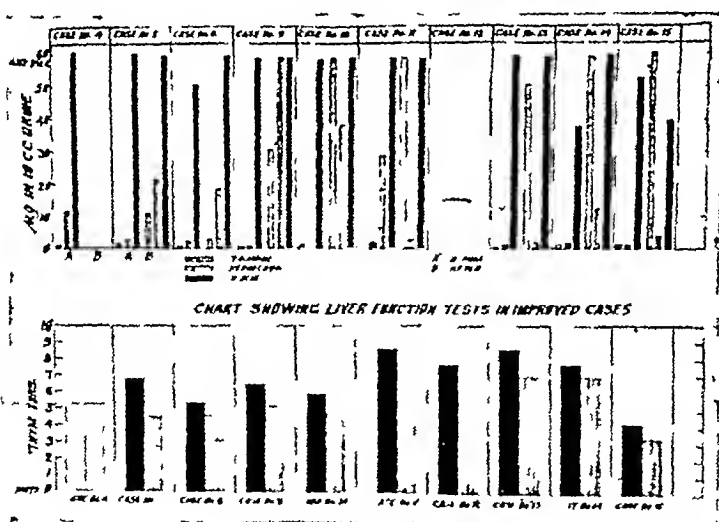


Chart 2

Two plasma protein estimations were done in every case one after the administration of casein hydrolysate and the other 4 days later on the termination of vitamin B complex administration. Though the second reading of plasma proteins was usually the same or slightly lower, the A/G ratio was very often improved, indicating the beneficial effect of these vitamins on the role of the liver in maintaining normal plasma protein relationships.

Those cases showing unimprovement of the albumin globulin ratio usually showed an improvement in the flocculation tests but not necessarily in the dye excretion ones. This is probably because the tests which showed improvement are supposed to be indicative of the dis-

turbance in the protein metabolism in the liver. This also emphasises the fact that no single liver function test has yet been discovered which can be used as a measure of total liver function. It is only by performing several of these tests that a cross-section of hepatic activity can be obtained.

Clearance Tests

(3) The clearance tests viz Bromsulphalein and Bilirubin seem the most sensitive to minimal improvements in liver function. This may probably be due to the fact that these tests reflect more the excretory activity of the liver rather than the cellular one. The obstructive changes would be expected to recover earlier than the parenchymatous damage.

Contrary to expectations, the thymol turbidity test seemed to bear a closer relationship to these clearance tests than to the cephalin cholesterol test. In 9 cases the thymol turbidity and the excretory tests showed change for the better, and in one case more did the latter show an improvement without a change in the flocculation test. The cephalin cholesterol test on the other hand improved only in 6 of the above 9 cases where the thymol turbidity and clearance tests had shown improvement of function. The close association of the thymol turbidity and the clearance tests is probably associated with the intimate inter-relationship of the parenchyma of the liver with the excretory system. Any slight alterations in the liver cells would also lead to intra-hepatic biliary obstruction and reflect themselves in changes in both the series of tests.

Flocculation Tests

(4) The cephalin cholesterol and thymol turbidity tests showed a discrepancy in 5 cases. Though both these tests are dependent on a qualitative change in the globulin fraction of the serum, it is believed that different fractions of the serum globulin independently influence the two tests. The altered serum globulin is again a manifestation of hepatic cellular dysfunction. In addition to the 6 cases where the cephalin cholesterol, thymol turbidity and the dye excretion tests showed a simultaneous improvement, there were 2 cases where the cephalin cholesterol improved alone, in one of these a rise in the A/G ratio could be a possible explanation but in the other there was no such change. As would be expected, from the intimate relationships of these tests to plasma protein fractions, the A/G ratio improved in majority cases with a better T/T response and in all except three cases where the Cephalin Cholesterol test had shown an improvement.

Cases which did not improve

The cases which did not improve were not apparently different in their selection from the cases which did. In attempting to explain this discrepancy of response, various possibilities were considered.

The Associated Presence of Protein Deficiency, Anaemia and Oedema

(a) The first consideration is the role that a coincident protein deficiency, anaemia or oedema might play in depressing the liver function of those cases which did not recover. It is true that the total plasma proteins and the albumin content was generally low in the cases selected but if one studies the tables given below one cannot find these levels to be lower in those cases which did not show any benefit than those which did.

	<i>Improved</i>	<i>Not Improved</i>
Total protein	4 375 to 6 56 gm	5 36 to 6 31 gm
Albumin	1 17 „ 3 8 „	1 72 „ 4 25 „
Globulin	2 21 „ 4 45 „	2 00 „ 4 5 „
Alb Glob ratio	1 1 8 „ 1 5 1 „	1 1 7 „ 2 1 „

There does not seem to be a sufficiently striking difference either in the total proteins or in the individual constituents or in the A G ratio in these two sets of readings to be able to explain the lack of conformity of response to the vitamin B complex on a basis of depressed protein levels

How much of the responsibility for the failure of certain cases to respond to the vitamin B complex can be ascribed to anaemia is again problematical. The variations in Hemoglobin in the two sets of cases was not striking

	<i>Improved</i> 38-70%	<i>Not Improved</i> 48-78%
Per centage Hb		

Before summarily dismissing anaemia and protein deficiency as insignificant influences in hepatic response it should be stressed that the duration of the deficiency state is of importance. It was difficult to determine the duration of these deficiencies and it was not unreasonable to assume that in those cases which did show improvement, the anaemia and hypoproteinemia had not been sufficiently long lived to set up irreversible changes in the liver, the reverse of this being equally true.

Oedema was a marked feature in only one case. Here cascain hydrolysate was given daily for 7 days till this had disappeared when liver function tests were performed. In the other cases where there was a transient swelling of the feet and legs, this had subsided before the first series of liver function tests were carried out. This factor was, therefore, never of a sufficiently severe order to interfere with the results. Moreover as far as improvement of liver function was concerned the behaviour of the oedematous and nonoedematous cases was equivocal as shown below

	<i>Improved</i>	<i>Not Improved</i>
No. of patients with oedema	3	3

Duration of Vitamin B Complex Deficiency

(b) Again the length of time during which the liver has been subjected to a deficiency of the vitamin B complex will necessarily influence the extent of the response to the administration of large doses of this vitamin. The longer this period of vitamin lack, the greater the chances of irreversible changes setting in and the more meagre the improvement with these vitamins.

Duration of Vitamin B Complex Administration

(c) In this series of investigations, the idea was to give saturating dose of vitamin B complex for a fixed period of 8 days and note the improvement in liver function. Perhaps in the more prolonged and severe cases, this may not have been of sufficient duration to effect a reversal of changes in the liver.

Possibility of Secondary Changes

(d) The fourth feature to be borne in mind is that perhaps as in Gillman's experiments the liver changes though initiated by a vitamin

deficiency may have in their turn set up secondary gastro-intestinal changes which help to perpetuate them. To carry the analogy further perhaps a primary replacement of gastric secretions (stomach extract) prior to vitamin therapy would prove efficacious in these cases.

The Role of Vitamin B Complex in Liver Function

The constituents of the vitamin B complex influence liver function and structure in two demonstrable ways (i) by their intimate relationship with carbohydrate metabolism, (ii) in the capacity of agents which mobilise liver fat viz lipotropic factors. There is however yet another action which is not clear. It has been found that preparations of yeast for example, improve liver function in a fashion which cannot be explained by the almost negligible lipotropic content.

Carbohydrate Metabolism and Vitamin B Complex

In this category are Thiamine, Riboflavin, Niacin and Adenylic acid. These are catalysts acting at various stages in the process of utilisation of glucose.

Thiamine

Thiamine in the form of its pyro-phosphoric ester (co-carboxylase) acts as a specific catalyst in the degradation of pyruvic acid. The conversion of vitamin B to its pyrophosphoric ester occurs partly in the tissues but to a large extent in the liver which also stores this enzyme.

There is convincing evidence of some relationship between vitamin B₁, glycogen storage in the liver and blood sugar levels after ether anaesthesia in rabbits, the usual depletion of liver glycogen can be nullified by administration of vitamin B₁ for three days prior to anaesthesia (Lauber 1939). It is assumed that the extra vitamin B₁ helps in the resynthesis of liver glycogen broken down by the anaesthetic.

Riboflavin

Riboflavin forms part of a complex oxidation reduction system for the metabolism of glucose, consisting of glucose (in the form of hexose-phosphate), flavoprotein, co-enzymes I and II, dehydrogenase and atmospheric oxygen as —

- 1 substrate + dehydrogenase → activated substrate
- 2 activated substrate + co-enzyme → reduced co-enzyme + oxidised substrate
- 3 reduced co-enzyme + lactoflavin → oxidised co-enzyme + reduced lactoflavin
- 4 reduced lactoflavin + O₂ → oxidised lactoflavin + H₂O

Nicotinic Acid

This constitutes part of coenzymes I and II which are intermediary in the oxidation and utilisation of glucose as shown previously.

Adenylic Acid

This portion of the vitamin B complex also forms a part of coenzymes I and II and it is believed to participate in the phosphorylation of glucose.

Lipotropes of the Vitamin B Complex

The origin of the concept of a lipotropic factor dates back to the years soon after the discovery of insulin. It was noted that if depancreatized dogs were kept alive with insulin they developed fatty infiltra-

tion of the liver which later went on to cirrhosis. This fatty infiltration could be prevented by feeding dogs with pancreas. Hershey and Soskin (1931) have shown that this infiltration could be equally well prevented by lecithin. It remained for Bestand Huntsman (1932) to prove that the active fraction of lecithin was choline. These workers further showed (1935), that casein had a like effect on fat removal from the liver. The hypotrophic action of casein is dependent on one of its component amino-acids, methionine. The pancreas however also possesses another active factor besides lecithin called lipocaine, the action of which is probably dependent on liberation of methionine from combination (Charkoff, Entenman and Montgomery, 1945) and rendering it available for hypotrophic action. Choline is by far the most hypotrophically active member of the vitamin B complex. Its activity is dependent on the fact that it possesses in its chemical structure loosely attached methyl- CH_3 radicals which are available for the conversion of liver fats into phospholipids (phosphorylation) an essential intermediary stage in fat transport in the absence of which fat accumulates in the liver and damages it. Goldblatt and Gyorgi (1935) showed that rats fed on a basal diet deficient in vitamin B complex but supplemented with vitamin B_1 , riboflavin and pyridoxine exhibited fatty infiltration and necrosis of the liver which could be prevented by the addition of yeast. They therefore concluded that liver changes of nutritional origin could be correlated to a deficiency of a part of the vitamin B complex other than thiamine, riboflavin or pyridoxine. The same workers in 1942 produced dietetic necrosis and cirrhosis in rats fed on a low casein diet with a high fat content and without choline. Administration of choline alone reduced the severity of the injury but administration of choline with cystine or of methionine prevented the injury altogether.

Other members of the vitamin B complex are also instrumental in the deposition or removal of liver fat. Thus thiamine is necessary for the development of fatty liver due to choline deficiency (Mc Henry, 1936). Biotin causes a considerable deposition of liver fat which is prevented by inositol but not by choline (Garvin and Mc Henry, 1940-41). Pyridoxine is said to exert a hypotrophic action (Gyorgi, 1944). A deficiency of riboflavin has been found to allow fatty infiltration of the liver.

Experimental Dietetic Liver Injury

Goldblatt and Gyorgi by their experiments thus brought about a complete reorientation of outlook on the pathogenesis of hepatic injury showing that this could be produced by dietetic imbalance alone. They paved the way for Himsworth and Glynn (1944) who brought forward evidence to the effect that there were two main types of liver injury that could be produced by abnormal diet in rats. With a diet deficient in protein particularly in cystine, the liver showed evidences of massive necrosis, later going on to post-necrotic scarring. On the other hand, with a high fat diet or with a deficiency of hypotrophic factors, the rats showed fatty infiltration and later a diffuse hepatic fibrosis. It is this second type of hepatic injury that is of interest to us in connection with the discussion today. The protective action of choline and of casein in the prevention of fatty infiltration has already been mentioned. The latter derives its activity from the presence of one of its component amino-acids viz methionine. Methionine like choline has a free methyl CH_3 group available for conversion of fat to phospholipids.

Clinical Examples of Dietetic Liver Injury

All the above data have been accumulated by dietetic experiments on animals. In human beings it is more common to obtain states of multiple deficiencies which upto now formed heterogeneous complexes defying systematic relationship of cause to effect. Thanks to intense experimental study, only an infinitesimally small fraction of which is presented above, many more clinical conditions are emerging from the cloak of mystery which once enshrouded them into the realms of rational thought.

Tropical Hepatomegaly

It is not a long stretch of imagination to take our minds from Himsworth's rats fed on a deficient diet to the inadequately nourished people of Asia and Africa, among whom fatty infiltration and cirrhosis are so common. According to Himsworth, most of these cases can be again put into one of two categories. Those of rapid development e.g. of acute massive necrosis with residual post-necrotic scarring (acute or subacute yellow atrophy resulting in multiple nodular hyperplasia) associated with cystine deficiency. Others of more insidious development e.g. fatty infiltration going on to diffuse hepatic fibrosis due to a deficiency of lipotropic factors. The work of Radhakrishna Rao (1935-36) on so called "infantile bilary cirrhosis" suggests that these cases again are examples of a dietetic deficiency of cystine or lipotropic factors, giving rise to a subacute toxic necrosis, the dietetic demands of the growth period accentuating the poverty of the diet. Toxic factors however can by no means be excluded in these cases of tropical hepatic fibrosis.

No discussion in the relationship of the diet to liver function would be complete without reference to the work of Gillman brothers in South Africa. A condition variously known as "Kwashiorkor", "Infantile Pellagra" or "Malignant Malnutrition" occurs among children in South Africa. It is characterised by dermatitis, oedema, angular and labial stomatitis, steatorrhoea, a macrocytic anaemia and a large fatty liver. These workers in following up cases with serial liver biopsies were able to show fatty changes going on to diffuse fibrosis in cases of long standing. This then was strong clinical support for what Himsworth had experimentally shown viz. that nutritional deficiency particularly of the elements of the vitamin B complex (particularly choline) was apt to produce a fatty liver, which condition was preliminary to a diffuse hepatic fibrosis. Gillman and Gillman found no improvement in these cases on treatment with vitamin concentrates and administration of liver extracts was only of slight benefit. They however discovered that with exhibition of powdered hog's stomach 10 gms per day, improvement was dramatic and in a few days liver fat was considerably depleted. This is just one of those numerous examples in the human economy where in a series of changes once initiated lose context with their etiological agents and themselves set off a train of secondary consequences which no longer responds to treatment of the prime cause.

Here, for instance, the immediate effect of the dietetic imbalance was a fatty infiltration of the liver and an upset of fat metabolism. This latter condition leads to a depression of secretion of gastric principles. At this stage vitamin therapy is ineffective whereas replacement of gastric extracts breaks the cycle and improves the condition. This may

provide explanation for those cases in our series which showed little or no improvement in liver function on saturation with vitamin B complex

Alcoholic Cirrhosis

The close association of cirrhosis of the liver with alcoholism, has been noted for many years. At one time, there was a tendency to consider the relations to be one of cause and effect. O'Connor has shown that diffuse fatty infiltration with an enlargement of liver can nearly always be demonstrated as an early change in alcoholism, and when this is persisted for some time a diffuse hepatic fibrosis sets in ultimately resulting in the finely granular shrunken liver of alcoholic cirrhosis. It is now generally conceded that the liver damage in chronic alcoholism is essentially dependent on a nutritional defect. Alcohol, itself deficient in lipotropic factors sets up a chronic gastritis with anorexia and achlorhydria resulting in a diminished intake and absorption of both lipotropic principles viz choline and of protein, the former being responsible for the preliminary fatty infiltration.

Diabetic Hepatomegaly

Again fatty infiltration of the liver and cirrhosis are not infrequent concomitants of diabetes mellitus. Here they are probably associated with a deficiency of lipocaine from the pancreas and also the heavy drain placed on the dietetic lipotropic factors as a result of the abnormal carbohydrate and fat metabolism. Indeed depancreatized dogs kept alive on insulin show fatty changes in the liver which if untreated go on to a diffuse fibrosis but which can be reversed by lipocaine and choline given in adequate amounts.

The Relationship of Fatty Infiltration to Diffuse Fibrosis

The relationship of fatty infiltration to diffuse fibrosis has been much discussed. It has been suggested by O'Connor that fatty infiltration is an essential preliminary stage to cirrhosis in alcoholic hepatitis. Again, as has been mentioned, in the depancreatized dogs and in diabetes, fatty infiltration always precedes the development of diffuse fibrosis. Himsworth has found a similar sequence of events in his choline deficient rats viz fatty infiltration going on gradually to a diffuse fibrosis. Both Himsworth and O'Connor conclude that the swelling of the parenchyma cells by deposition of fat leads to a narrowing of the sinusoids, impeding the interlobular circulation, the blood as it passes slowly through the sinusoids is deprived of its nutrients and oxygen almost completely by the time the centre of the lobule is reached and the cells situated here gradually degenerate and disappear. At the same time the anoxemia leads to connective tissue proliferation resulting in a diffuse fibrosis. Furthermore, it is immaterial with what substance the cell is infiltrated, be it glycogen or cholesterol as in disturbed metabolic processes, or silica-gels as in the experimental animal, the process is a purely mechanical affair, in every case there is an obstruction of the interlobular circulation resulting in malnutrition and degeneration of the parenchyma and later to a fine fibrosis.

All these clinical examples of hepatomegaly discussed above viz "Tropical Cirrhosis", "Alcoholic Cirrhosis" and "Diabetic Hepatomegaly", illustrate the effect of a deficiency of lipotropic factors such as choline and also incidentally of proteins on liver health. As choline is considered to be an important factor of the vitamin B complex they serve

to emphasise the role of these vitamins in maintaining normal liver structure and function

SUMMARY AND CONCLUSIONS

(1) An attempt has been made to assess the effect of large doses of vitamin B complex on the liver function of individuals showing evidences of deficiency of these vitamins clinically and on urine analysis

(2) In 10 cases, out of the 15 investigated, there was an improvement of liver function

(3) A correlation of the tests of liver function carried out in the present series reveals that the bromsulpholein and bilirubin tests are most sensitive for they showed improvement in all the 10 cases. The thymol turbidity and cephalin cholesterol tests seemed also of value being improved in 9 and 6 cases respectively. The A/G ratio improved in 9 cases and in 5 of these cephalin cholesterol test also showed a change for the better, indicating the intimate inter-relationships of these tests. The close association of the thymol turbidity with the excretion tests is discussed

(4) In 5 cases, oedema was present in spite of the fact that the plasma proteins and serum albumin were above the critical level for oedema

(5) An assessment of niacin alone in the urine, in no way indicate the degree of saturation of the body with this vitamin

(6) The role of vitamin B complex in liver function and the possible relationships of a deficiency of these vitamins to fatty infiltration and diffuse fibrosis of the liver are discussed

BIBLIOGRAPHY

- BEST C H, GRANT R and RIDOUT J H
- BEST C H, HERSHEY J M and HUNTSMAN M E
- BEST C H and HUNTSMAN M E
- BEST C H and HUNTSMAN M E
- BEST C H, LUCAS C C, PATTERSON J M and RIDOUT J H
- CHAIKOFF I L, ENTENMAN C and McHENRY E W
- CONNOR C L
- CONNOR C L
- DU VIGNEAUD V, CHANDLER J P, COHN M and BROWN G B
- DU VIGNEAUD V, CHANDLER J P, MOYER A W and KEFFEL D M
- DU VIGNEAUD V, COHN M, CHANDLER J P, SCHENK J R and SIMMONDS S
- FOUTS
- GAVIN G and McHENRY E W
- GAVIN G and McHENRY E W
- GAVIN G and McHENRY E W
- GILLMAN J, GILLMAN T, MANDLESTAM J and GILBERT C
- GILLMAN J and GILLMAN T
- GILLMAN J and GILLMAN T
- GILLMAN J and GILLMAN T
- GYORGY P
- GYORGY P and GOLDBLOTT H
- GYORGY P and GOLDBLOTT H
- HERSHEY J M
- HERSHEY J M and SOSKIN S
- HIMSWORTH H P and GLYNN L E
- HIMSWORTH H P and GLYNN L E
- HIMSWORTH H P and GLYNN L E
- HIMSWORTH H P and GLYNN L E
- HIMSWORTH H P and GLYNN L E
- McHENRY E W
- McHENRY E W and PATTERSON J M
- RADHAKRISHNA RAO M V
- RADHAKRISHNA RAO M V
- SINCLAIR
- WILLIAMS C D
- J Physiol 1936 86 337
- J Physiol 1932 75, 56
- J Physiol 1932 75, 405
- J Physiol 1932 83 255
- Biochem J 1946 40, 368
- Biochem J 1945 160, 480
- Amer J Path 1938 14, 347
- J Amer Med Assoc 1937 112, 387
- J Biol Chem 1940 134, 787
- J Biol Chem 1930 131, 57
- J Biol Chem 1941 140, 625
- J Nutrition 1943 25, 217
- J Biol Chem 1941 132 41
- J Biol Chem 1941 139, 485
- J Biol Chem 1941 141, 010
- Brit J Exp Path 1945 36, 07
- Archiv Path 1945 40 239
- Archiv Intern Med 1945 76, 03
- J Amer Med Assoc 1945 129, 12
- Amer J Clin Path 1944 14, 67
- J Exp Med 1942 75, 355
- Proc Soc Exp Biol Med NY, 1911, 46, 492
- Amer J Physiol, 1930 93, 657
- Amer J Physiol 1931, 98, 74
- Lancet 1944 1, 457
- Clin Sci, 1944 5, 93
- Clin Sci 1944 5, 133
- J Path and Bact 1944, 56, 297
- J Physiol, 1936 86, 27
- Physiol Review 1944 24, 128
- J Ind Med Assoc 1936 7 6, 304
- Ind J. Med Res 1935 6, 6, 89
- Rec Adv Cl Path 1947
- Lancet 1935 11, 1151

Critical Notes and Abstracts

MEDICAL PROGRAM OF THE ATOMIC ENERGY COMMISSION

Dr Shields Warren in a recent discussion of the medical program of the Atomic Energy Commission points out that ionizing radiation may affect the body in two ways first, as an external radiation such as from the conventional X-ray tube, secondly, as an internal radiation such as occurs from the administration of radioactive substances. It is stated that there is no way to tell by the examination of a single cell or tissue whether the radiation effect has been produced by neutrons, by 200 kilovolt roentgen rays or by the gamma rays of radium.

The predominating effect that occurs is assumed to be brought about through interference with the nucleic acid of the cell. In internal radiation because of the specific affinity of certain tissues for specific elements and because of the relatively short range of many of the types of radiation emitted by various isotopes, some degree of selective localized radiation may be obtained.

In determining the therapeutic value of any radioactive isotope, several factors must be taken into consideration. First, the inherent toxicity of the substance itself. Secondly, the half-life of the material, "material which has a long half-life is much more dangerous from the standpoint of possible excessive radiation than one with a short half-life." Thirdly, the degree of localization is important, for example, radioactive sodium is relatively limited in use because of the high degree of diffusibility of the ion. Fourthly, the range and type of radiation which tend to limit the region effectively irradiated to the vicinity of localization is important. Fifthly, the element must be such that its specific activity is reasonably high preferably about 1 millicurie per milligram of element. Doctor Warren indicates that there are relatively few substances that fulfil all these desirable criteria.

The medical program of the Atomic Energy Commission is discussed. The program is divided into four sections: one, the maintenance of health of the workers of the Commission and its contractors, second, protection of environmental health involving such problems as waste disposal and possible contamination of surrounding areas, third, the development of surrounding research in problems peculiarly related to atomic energy itself, and fourth, direct cancer research with the very short-lived radioactive isotopes that are available at the various installations of the Atomic Energy Commission.

The Atomic Energy Commission is also conducting a fellowship training program under the auspices of the National Research Council and provides up to 100 pre-doctoral fellowships and 75 post-doctoral fellowships annually. The pre-doctoral fellowships can be made available to medical students who desire to interrupt their training at the end of the second year to undertake a year of fundamental research in this new field.

(Warren Shields, Boston, Mass. Medical Program of the Atomic Energy Commission. Journal of the American Medical Association 138: 1227-1228, December 23, 1948.)

VITAMIN K AND ITS EFFECT ON DICUMAROL-INDUCED HYPOPROTHROMBINEMIA

In a recent report by E. J. Boyd and E. D. Warner, dealing with the effect of vitamin K on dicumarol-induced hypoprothrombinemia, a two-stage method of prothrombin determination was used. By this method, the conversion phase is separated from the clotting phase, eliminating the rate of conversion of prothrombin to thrombin as a factor in prothrombin measurement. The authors considered this method more reliable, since the one stage method is objectionable in that it depends not only on the concentration of prothrombin but also on the rate of conversion of prothrombin to thrombin.

Adult albino rats of the Sprague-Dawley strain were used. They were maintained on a diet which contained adequate amounts of vitamin K, since it was considered desirable to parallel as closely as possible clinical conditions in which the diet is not likely to be deficient in vitamin K, and to measure prothrombin concentration only. Dicumarol and menadione were given by stomach tube, and Hykinone was given by intraperitoneal injection. Both the vitamin K preparations and Dicumarol were given as daily doses. Prothrombin titration by the two-stage method was performed on the plasma.

The great variation in clinical result is, in the opinion of the authors, due to the wide diversity of methods used to estimate prothrombin and the lack of control possible only in experimental animals. There also is evidence that the dilute plasma technique has much greater standard deviations on duplicate determination than do whole plasma techniques. The possibility that vitamin K affects factors which govern prothrombin conversion as well as those which control its concentration is considered. This could explain the protective action of vitamin K against Dicumarol which has been reported by workers using the one stage method. The prothrombin level, as determined by the two-stage method, varied considerably, in rats treated with Dicumarol. There was definite recovery phase soon after the initial fall in prothrombin caused by Dicumarol. It was found that menadione and menadione bisulfite in large doses had no detectable counteracting effect on the prothrombin level of rats.

(Boyd E. J. M.D. Iowa City, Iowa, Warner E. D. M.D. Effect of Vitamin K on Dicumarol Induced Hypoprothrombinemia in Rats. The Journal of Laboratory and Clinical Medicine November 1948. Warner E. D. Brinkhous K. M. and Smith H. P. A Quantitative Study on Blood Clotting Prothrombin Fluctuations Under Experimental Conditions, American Journal of Physiology 114: 667 1936. Warner E. D. Brinkhous K. M. and Smith H. P. The Prothrombin Conversion Rate in Various Species. Proc. Soc. Exper. Biol. and Med. 40: 197 1930.)

INTRAVENOUS OXYGEN IN BRONCHIAL ASTHMA

Markow, et al, recently studied the effect of intravenous oxygen in a series of nine cases of severe bronchial asthma. The oxygen was administered in amounts ranging from 8,000 to 22,000 c.c. in one, two or three stages. The oxygen was usually given just after the onset of an attack. Vital capacities in all cases were increased from 800 c.c. to 1,800 c.c. or from 80 to 87 per cent. In all cases there were some degrees of immediate clinical relief, appearing from five minutes to two hours after therapy. This was evidenced by lessening of dyspnea and wheezing respiration. Some improvement, for a minimum of at least ten days, followed the treatment. However, in five of the cases who received from 8,000 c.c. to 22,000 c.c. of oxygen, clinical improvement was maintained for from four to six months.

The absence of untoward incidents in the treatment was believed by the author to be due to the slow administration and the low pressure of the flow of oxygen. In this case, the Zeigler technic and apparatus with 200 percent (commercial) oxygen was used. Oxygen was administered at the rate of 600 c.c. per hour at a pressure just slightly above venous pressure. The oxygen was allowed to flow for periods from two to 17 hours without interruption except when it became necessary to clear the needle of an occasional clot. The authors were unable to determine whether or not the intravenously injected oxygen acts therapeutically in a manner similar to inhaled oxygen or whether some other therapeutic quality of oxygen itself was producing an effect.

(Markow Harry et al, Beth El Hospital, Brooklyn, N. Y. Effect of Intravenously Administered Oxygen on Symptoms and Vital Capacity in Bronchial Asthma. *Annals of Internal Medicine* 29: 607-622 October, 1948.)

A STUDY OF PSYCHIATRIC NEEDS IN REHABILITATION

The New York City Committee on Mental Hygiene recently studied the extent and nature of psychiatric problems among men in New York City excluded from military service for neuropsychiatric disabilities. They proposed to determine the severity of handicapping, the numbers needing psychiatric help, the kinds of psychiatric help needed and the possibilities of reducing the gap between present needs and present resources for psychiatric aid. The study was made by interviewing 314 men rejected and 309 men discharged for neuropsychiatric disabilities. These were selected from ten selective service boards.

Ten categories of disturbance were studied. However, the large majority of cases fell within the first two groups, that is, psychoneuroses and inadequate psychopathic personality. Among other interesting facts developed in the study, it was discovered that many of the men demonstrated to need psychiatric aid refused treatment because of the fear and scorn popularly associated with psychiatric disorders. The mention of psychiatry still suggests to most persons the "frightening implications of insanity and lunatic asylums." Interview responses from patients needing treatment contained rubber stamp phrases such as "nut doctor" for psychiatrists, and "Don't tell me I'm loco," and "I'm not wacky."

Many patients during the course of the interview expressed great relief at the assurance that they were not "crazy" or "slaphappy" and subsequently agreed to undertake extended treatment. Many who are unwilling to admit the psychiatric nature of their complaints were willing to take medical treatment but not psychiatric treatment. The gap revealed between numbers of discharges needing psychiatric help and those who would accept it was painfully large. However, the gap between those who needed help and those receiving it was much greater.

Of those who needed help, only 26 percent were willing to accept it and only 5 percent were actually receiving psychiatric aid. Furthermore, 61 percent of the men who need and want psychotherapy require free service and the remaining 39 percent, with but few exceptions, could pay for only low cost care. The authors concluded that greatly increased budgets and staffs will be imperative for supplying even partially adequate service. However, given the necessary insight,

training, determination and recognition of what is required, much can be done even under present limitations

(Psychiatric Needs in Rehabilitation—A Study by the New York City Committee on Mental Hygiene of the State Charities Aid Association, New York N.Y. 1948)

AUREOMYCIN THERAPY IN HUMAN BRUCELLOSIS

Spink, et al, report a study and observations made in 24 patients with human brucellosis who were treated with aureomycin. In all 24 patients one or more positive cultures of *brucella melitensis* were obtained. There were 16 female and eight male patients and the duration of illness varied from a few days to a year. Six of the 24 patients had been previously unsuccessfully treated with streptomycin or with combined streptomycin and sulfadiazine. At first the patients were treated with one half Gm of aureomycin every six hours coupled with 1 to 3 Gm of sulfadiazine daily for a period of 13 days.

Results obtained with this group were so successful that eight patients were subsequently treated with aureomycin alone with equally good results. Every patient was febrile before treatment started and temperature returned to normal two to three days after initiation of treatment. Two of the patients were subsequently treated a second time because of recurrent fever in spite of the fact that blood cultures had remained negative. No serious toxic complications resulted from aureomycin therapy. However, 12 of the 24 patients experienced a sudden rise in temperature eight to 12 hours after the first oral dose. The only other side effects noticed were occasional nausea, vomiting and mild diarrhea. These manifestations were transitory.

The authors concluded that in spite of the excellent and encouraging results produced by aureomycin in these series of cases, that they are only now considering the immediate therapeutic value of aureomycin and that a long period of follow-up study will be necessary in order to completely evaluate the drug for this disease. The patients are now being closely followed and a statement concerning the possibility of bacteriologic relapses will be made at a later date.

(Spink, Wesley W. et al. Aureomycin Therapy in Human Brucellosis due to *Brucella Melitensis*. Journal of the American Medical Association, 138: 1145-1148, December 18, 1948.)

OPTIMAL DOSAGE AND METHOD OF ADMINISTRATION OF DIGITOXIN

A recent investigation concerning the optimal dosage and method of administration of digitalis glycosides was made by Harold J. Stewart and Abbott A. Newman. In their studies with digitoxin, they chose slowing of the ventricular rate as a satisfactory guide to digitalis effect. Patients with auricular fibrillation were studied for this purpose. The authors attempted to reduce the rapid ventricular rate in auricular fibrillation in 24 hours to around 70 to 75 per minute, which is the rate considered optimal for therapeutic purposes. The amount of the drug, which by complete absorption in 24 hours will slow the ventricular rate to around 70 to 75 per minute would be considered optimal for clinical use of the drug. This appears to be approximately the same for all adult patients irrespective of body weight.

The therapeutic digitalization in patients with normal sinus rhythm, in whom there is not the guide of heart rate as in patients with auricular digitalization, could then be achieved by using the same amount of the drug that slowed the ventricular rate in patients with

auricular fibrillation to around 70 to 75 per minute. Spreading the amount of the drug to be given for full digitalization over a period of 18 hours does not increase the amount of the drug needed, because excretion during the first 24 hours can be neglected for clinical purposes, or at most could only make the difference of one daily maintenance.

A review of the records of 22 hospital patients who had auricular fibrillation for which they received digitoxin disclosed that 1.2 mg of the drug given within a 24 hour period, generally failed to reduce the heart rate to between 70 and 75 per minute. The records of patients suffering from hyperthyroidism were excluded, since larger amounts of digitalis are required to achieve slowing of the ventricular rate. The dose of 1.2 mg was considered to be inadequate given orally or intravenously.

The authors are of the opinion that insistence upon 1.2 mg as the average full therapeutic digitalizing dose of digitoxin is most unfortunate, lulling physicians into a false sense of security, when patients have secured full benefits from the use of the drug. They have stated that the average maintenance amount of digitoxin should range between 0.1 and 0.2 mg. Acceptance of the maintenance dose of 0.2 mg is considered hazardous for daily use since instances of toxic effects after some months of such usage are now coming to light. In conclusion, the authors add that it is more difficult to keep patients in equilibrium maintenance dose of digitoxin than with the whole leaf.

(Stewart Harold J, New York City, N.Y. Newman Abbott A. The Amount of Digitoxin (Digitaline Native) Required for Adequate Digitalization, *American Heart Journal* November, 1948. Stewart, H. J. Crane N. F. Deltrick J. E. and Thompson, W. P. Action of Digitals in Compensated Heart Disease, *Archives of Internal Medicine* 62: 547 1948.)

THE ADRENOCORTICAL FUNCTION AND ITS POSSIBLE RELATIONSHIP TO THE LEUKEMIC STATE

The purpose of an investigation by Dr. Louis Levin was twofold: (1) to determine, by available criteria, the degree of activity of the adrenal cortex of animals suffering from lymphatic leukemia, (2) to attempt inhibition of the development of transmitted lymphatic leukemia by the administration of 11-dehydrocorticosterone, the only pure adrenocortical steroid available in sufficient amount. The animals were kept under constant, adequate conditions until the leukemic syndrome, whether spontaneous or transmitted, was definitely established. The mice used were the inbred leukemia susceptible AK strain of Furt.

When indications of leukemia were apparent, the animals were autopsied. No animal was included in the leukemia groups unless there was definite hypertrophy of the spleen and lymph nodes. The weights of the spleen, lymph nodes, and liver were good indexes of whether or not leukemia was present. The adrenals were immediately covered with 2 ml of acetone-alcohol (1:1), finely ground with the aid of a small amount of sand and a stirring rod.

The extraction with the hot acetone-alcohol mixture was repeated three times. The extract was then cooled and filtered. An aliquot of the filtered solution was used for total cholesterol determinations by the Sperry-Schoenheimer method. When mice were treated with 11-dehydrocorticosterone, they received daily subcutaneous injections of the steroid, beginning at the time the animals were inoculated to the

time of autopsy The author considers the administration of 11-dehydrocorticosterone to have had little or no effect on the development of the leukemic syndrome, since the effect of the 11-dehydrocorticosterone treatment on the adrenal cholesterol concentration apparently partially prevented the decrease in adrenal cholesterol accompanying the leukemic syndrome in the AK strain mice, but in the AF leukemic mice, such treatment did not prevent the loss of adrenal cholesterol

Although 11-dehydrocorticosterone has a good glycogenic effect in mice, it is possible that it is not so effective in preventing development of leukemic changes as, for example, 11-dehydro-17-hydroxycorticosterone, the compound reported by Heilman and Kendall to inhibit the growth of mouse lymphosarcoma It is also conceded possible that the adrenal changes observed are merely the expression of a reaction to the stress of the disease process on the organism as a whole, and that other criteria of adrenocortical activity must be studied before a direct relation between the adrenal cortex and the development of leukemia may be considered as established

(Levin Louis Ph D On the Possible Relationship Between Adrenocortical Function and the Leukemic State Cancer September 1948 Furth J and Strumia M Studies on Transmissible Lymphoid Leukemia of Mice Journal of Experimental Medicine 53 715 781 1931 Sperry, W M Publication of the New York State Psychiatric Institute 1942 Heilman F R and Kendall E C Influence of 11 dehydro-17 hydroxycorticosterone (compound F) on Growth of Malignant Tumor in the Mouse Endocrinology 34 416 420 1944)

METABOLISM, TOXICITY, AND MANNER OF ACTION OF GOLD COMPOUNDS IN THE TREATMENT OF ARTHRITIS

An intensive study of the metabolism and toxicity of the various gold compounds used is presented by Walter D Block, Ph D, Naomi C Geib, MS, and William D Robinson MD, under the auspices of the Rackham Arthritis Research Unit, Medical School, University of Michigan It was found that when gold compounds are injected intramuscularly into white rats, the gold is deposited in various tissues of the body, primarily in the liver and kidney The amount and site of deposition seem to depend on the physical properties of the compound studied

The authors became interested in whether the respiration of these tissues as measured by oxygen consumption is influenced by the presence of gold and whether a correlation exists between the concentration of gold in the tissue and its rate of respiration If such a relationship did exist, it might provide an insight into the mechanism of gold toxicity Using the Warburg technique, it was found that the oxygen consumption of rats in the kidney and liver slices was inhibited in vitro by the inorganic compounds, gold chloride and gold sodium thiosulfate The in vitro inhibition of oxygen consumption of rat kidney slices observed with gold sodium thiosulfate is not lessened by the potential thiol compounds cystine and methionine, nor by BAL or thiomalic acid having thiol groups, however sodium thioglucose does lessen the inhibition of oxygen consumption

The effects of BAL and thiomalic acid may be masked by the fact that these compounds in themselves produce inhibition of respiration The in vitro inhibition of oxygen consumption of rat kidney slices caused by gold chloride is appreciably reduced by thiomalic acid, BAL, L-cystine, and sodium thioglucose, but not by methionine or sodium thioester

When three thiol groups are furnished for each atom of gold, the reduction of inhibition is more clearly shown than when only one thiol group per atom of gold is present.

It appears that under conditions of these experiments, there is a chemical reaction in vitro between gold chloride and thiol groups to produce a compound which does not inhibit tissue respiration. Gold chloride is extremely toxic and has not been used in treating human beings. Yet it is the only salt which, under the conditions of this study, appears to be detoxified by various thiol groups. The ability of thiol groups to remove gold deposited in tissues has not been investigated by the authors in their study, but their work has shown the ability of thiol compounds to lessen the in vitro inhibitions of oxygen consumption when the compounds are used simultaneously with certain gold salts.

(Block, Walter D. Ph.D., Geib, Naomi C. M.S., and Robinson, William D. M.D., Ann Arbor, Michigan: Metabolism, Toxicity and Manner of Action of Gold Compounds in the Treatment of Arthritis, the Journal of Laboratory and Clinical Medicine, November 1948)

EFFECTS OF CURARE AND PROSTIGMINE ON THE CENTRAL NERVOUS SYSTEM

Preliminary observations in a recent report by Sidney Bernian suggests that curare, known for its paralyzing action on the neuromuscular junction in skeletal muscle, and prostigmine, which enhances neuromuscular transmission, have depressant effects on the central nervous system independent of their mutually antagonistic peripheral effects in muscle. The author deemed it important to present the findings of early clinical observations regarding the central effects of curare on humans, in view of the mounting interest in the therapeutic applications of curare in poliomyelitis, spasticity, tetanus, shock therapy and anesthesia.

Nineteen patients received a course of prostigmine injections alone, 18 received curare alone, and finally 14 received prostigmine and curare in combination. The injections were given 3-4 hours after arising in the morning following which both ambulatory and bed patients were encouraged to resume their usual activities. Prostigmine, methyl sulfate, 10 mg was injected subcutaneously. Intocostrin, a water soluble, purified tubocurarine was injected intra-muscularly in doses ranging from 0.6 mg per kilogram to 1.0 mg per kilogram and in some cases up to 1.5 mg per kilogram. Data regarding the status of the deep reflexes, spasticity and clonus, were obtained by means of frequent neurologic examinations.

The three manifestations of hyperactivity changed singly, or in combination, and not to similar degrees. Reflex changes and clonus measurements were most sensitive in response, and these with spasticity, as spasticity decreased, voluntary motor power increased.

Eight out of 19 patients receiving 1 mg of prostigmine revealed an increase of neuro muscular activity as measured by spasticity, reflexes and clonus. One early diminution effect and five, protracted relaxation effect. Anti-spastic effects were observed in five patients after injection of 1 mg of prostigmine in one case lasting as long as 68 hours. A sedative effect was observed in 16 out of 19 patients receiving curare alone in small doses up to 1 mg per kilogram. Nine out of 18 patients receiving curare alone showed an augmentation of neuromuscular activity. Therapeutic relaxation was noted with

curare alone in one case of hematomyelia, one of dystonia musculorum deformans, one of Friedrich's ataxia, two of multiple sclerosis

Ten out of 14 patients receiving the combination of curare and prostigmine demonstrated an augmentation of neuro-muscular activity and five of this group showed the protracted relaxation effect. Many points are controversial. Complicating factors are the ocular muscle imbalance, heaviness of the lids, and muscular relaxation. The author quotes clinical observations of Whitacre and Fisher who have achieved with the use of curare as the sole anesthetic agent complete anesthesia as an additional argument for the hypothesis of a central action of curare.

The author concludes that sufficient clinical support to the laboratory evidence has been given that in addition to its peripheral paralytic action, curare has an independent action on the central nervous system, probably a depressant action maximally on the subcortex.

(Berman S. Detroit, Mich. The Effects of Curare and Prostigmine on the Central Nervous System. Connecticut State Medical Journal. December 1948. Bennett A. E. Curare in Convulsive Shock Therapy, The Trained Nurse and Hospital Review. March 1940. Cullen S. C. Clinical Laboratory Observations on Use of Curare During Inhalation Anesthesia. Anesthesiology 5: 166-171. March 1944. West R. Curare Pharmacology. Proc Roy Soc Med. vol 28 pp 505-578. 1935. Whitacre R. J. and Fisher A. J. Clinical Observations on the Use of Curare in Anesthesia. Anesthesiology, vol 6, March 1935.)

TISSUE EXAMINATION IN RHEUMATOID ARTHRITIS

The presence of nodular inflammatory lesions in skeletal muscles of patients with rheumatoid arthritis and similar lesions described in other diseases led Steiner and Chason to determine from biopsy material the incidence of cellular infiltrations in other diseases. Attempt is made to establish differential diagnosis on histologic appearance of polymyositic nodules in rheumatoid arthritis. Sections from the gastrocnemius and deltoid muscles and occasionally from other skeletal muscles were studied in 27 patients with typical rheumatoid arthritis.

For controls skeletal muscle was taken from 126 other patients in which cellular infiltrations might be expected to occur. All the muscle specimens were taken either at biopsy or during amputations. Tissues were routinely fixed in formalin and stained with hematoxylin and eosin. Multiple sections and special stains were made whenever indicated. Control tissue was taken from 12 normal persons, 70 patients with atherosclerosis, and gangrene, also diabetes, 16 patients with disseminated lupus erythematosus, four with thromboangitis obliterans, four with dermatomyositis, four with trichinosis, four with scleroderma, six with miscellaneous disease of muscle, and six with non-rheumatoid polyarthritis (including one with rheumatic fever).

In the clinically typical rheumatoid arthritis, nodular infiltrations were composed most commonly of an inner group of lymphocytes with an outer layer of irregularly disposed plasma cells. Some of the larger nodules contained an inner core of cells of epithelioid appearance. Such nodules were found in 26 of the 27 rheumatoid arthritis patients. Nodules were sharply circumscribed and were always located in the endomysium and/or the perimysium and rarely in the epimysium. Adjacent muscle fibers revealed varying degrees of degenerative change which was secondary to the inflammatory reaction. The single case in which nodular infiltration was not found was that of a 74-year old woman who had had arthritis for over 30 years. The histopathologic

characteristics of the infiltrates were such that differential diagnosis could be made without difficulty

In six of seven patients with disseminated lupus erythematosus in whom cellular infiltrations were present, the muscle lesions were differentiated. In the seventh patient the lesions were so similar that differential diagnosis was not possible. Histopathologic differentiation was easily made in 125 of the 126 controls. In the controls, infiltrations were usually poorly circumscribed and often appeared to be extending into the muscles. Infiltrates were composed either of neutrophils only, or of a diffuse mixture of neutrophils and lymphocytes and sometimes a few scattered phagocytes, eosinophils, and plasma cells. In all patients in whom cellular infiltration was found, joint pains were a prominent symptom.

(Steiner Gabriel M D and Chason J L M D Differential Diagnosis of Rheumatoid Arthritis by Biopsy of Muscle American Journal of Pathology Vol 18 No 12 p 931, December, 1948)

EFFECT OF ATABRINE ON CARDIAC ARRHYTHMIAS

The authors discuss the physiologic and pharmacologic properties of atabrine and quinidine, which are shown to parallel each other closely. Twenty-six patients with auricular fibrillation were treated with atabrine with successful results in 13 of 27 trials. Included in the 14 patients in whom atabrine was unsuccessful were five patients with thyrotoxic heart disease and one patient with fatal pheochromocytoma with rheumatic heart disease.

Quinidine administered before atabrine was used was ineffective in 16 trials. In those patients in whom atabrine failed to restore a normal rhythm digitalis and/or quinidine was of no avail in all but one instance. Six patients with cardiac arrhythmias other than auricular fibrillation were treated with atabrine, included were two cases each of nodal tachycardia, auricular flutter, and ventricular tachycardia.

Atabrine was successful in three of these six cases, two of the unsuccessfully treated patients died shortly after treatment, and autopsy revealed coronary occlusion. The best results with atabrine therapy occurred in older patients with arteriosclerotic cardiovascular disease and in younger patients in whom the arrhythmia was of less than 48 hours' duration. The time at which the arrhythmias disappeared after atabrine therapy approximated the time at which the maximal blood levels were reached following intramuscular injections of atabrine. The number of patients in whom cardiac arrhythmias were successfully treated with atabrine is too small to permit the use of Pearsonian techniques but large enough to merit further observation and trial of this drug.

(G riller Menard M Boston Mass and Volinlem Stephen B : The Effect of Atabrine (Quinidine Hydrochloride) on Cardiac Arrhythmias American Heart Journal 37 79 91 January, 1949)

USE OF ISOTOPES IN MEDICINE

Paul C. Aebersold, Ph D, furnishes specific data on distribution of isotopes for medical and biological purposes during the past two years. Isotopes were distributed from Oak Ridge, Tenn. From August 1946 through May of 1948, 21,103 shipments of isotopes for study in animal and human physiology and medical therapy were made. Forty-three institutions are now using phosphorus of P-32 for medical therapy, 38 institutions are using iodine in medical therapy, 119 institutions are

using several of the isotopes in all fields of study including investigative and therapeutic application

Over 70 per cent of all shipments have been for investigation in therapy and human physiology, the remaining fields of study have been in chemistry, physics, industrial research and metallurgy. Of those used more in medical therapy, I-131 and P-32 account for the greatest part inasmuch as the half-life of these I-131 (eight days) and P-32 (14 days) permit a much greater rapidity of decay and therefore shipments are required more frequently. Isotopes are being shipped to 30 states in the United States, the largest amount is at present going to Massachusetts. Illustrations of uses of C-14 in metabolic studies include (1) Protein metabolism with labelled amino acids—leucine, glycine, lysine and amino adipic acid, alanine (2) Carbohydrate metabolism with labelled intermediates such as lactic, pyruvic, oxalacetic and propionic acid and (3) Fate of labelled fats.

Other illustrations of uses of P-32, S-35, Ca-45 are also mentioned. The author mentions the fact that investigators in foreign countries can obtain isotopes by application through the Commission. Twenty-nine radioisotopes of 20 elements which are of particular value in biologic and medical studies are available. It is stated that although international distribution has been in effect only 10 months, shipments have already been made to 14 countries. The author considers that these studies are opening a new field for specialization known as "isotapology." Although the use of these substances can be fraught with hazard there has been collected a large amount of knowledge on how to control them and with this knowledge and a healthy respect for the materials to be handled, safe conditions of work can be easily established.

(Leberhold, Paul C. Oak Ridge, Tenn. Isotopes for Medicine. Journal of the American Medical Association 133: 1222-1225 December 1948.)

HORMONAL TREATMENT OF CANCER

It is generally known that the only hope for cancer depends on the complete destruction or removal of the tumor cell, but cure is difficult, if not impossible, when metastases occurs. Therefore, chemotherapy has been resorted to, experimentally, in an effort to find a cure that can be adapted to such a task. McCullagh, in a recent paper, states that sex hormones have shown more promise than any other form of chemotherapy. He warns that hormonal treatment of cancer is not without dangers, however, if it is used in improperly selected cases, and that the treatment is palliative, not curative.

In properly selected cases, the treatment is stated to relieve pain, improve health and prolong life. According to Greer profound changes in the breast are frequently in association with certain ovarian or testicular tumors, in some tumors of the pituitary and adrenal cortex, as well as breast hypertrophy in cirrhosis of the liver, malnutrition, in some instances, and during stilbestrol therapy for prostatic cancer. Under some circumstances mammary enlargement occurs in association with testicular failure as well as in eunuchoid men treated with testosterone.

There are a few reports of the development of human breast cancer following prolonged administration of estrogen, but it is stated that with the widespread use of estrogens more reports of breast cancer would be expected, if they were important as a cause. The patients who

improve by the castration effects of the X-ray are almost entirely in the premenopausal group and unfortunately, beneficial response is considered transient. When it was discovered that certain carcinogenic hydrocarbons influenced the growth of experimental malignant lesions, some of these substances were tried in cases of human breast cancer. Although it would appear unlikely that excessive rate of growth of malignant breast tissue should be decelerated by substances which at one time accelerated the development of the same tissues, but such is the case.

Although favourable reports have been published on cases treated with triphenyl cloethylene, triphenylmethyle, hexestrol and diestrol, stilbestrol is still the most widely used estrogen. Undesirable side effects of estrogen therapy may include loss of appetite, nausea, vomiting, diarrhoea, and sometimes edema, which may be important when the myocardium is impaired. When high dosage is long continued, menorrhagia is likely to supervene. Good results include regression of the primary tumour, of soft tissue recurrences and of lymph gland and pulmonary metastases. Pain from skeletal metastases may be relieved, but favourable response in them, otherwise, is doubtful. There is great individual variation in response, but in all instances improvement is transient.

The chief danger of estrogen therapy is that growth of an existing cancer may be accelerated in younger women. In general, androgens have been found most useful in younger patients and in those who have skeletal metastases. Among the most impressive changes following testosterone therapy is a change in the roentgenologic appearance of skeletal metastases. In some patients areas of demineralization become denser, suggesting deposition of new bone. The untoward effects of stilbestrol therapy in men may include nausea, vomiting, the nipples and areolae become dark, and a striking degree of gynecomastia appears. Castration and estrogen treatment for prostatic cancer should not replace surgery where surgery holds any promise of cure. Impotence is also the rule when stilbestrol therapy is used in men. In general the results of treatment with stilbestrol, though slower, are considered otherwise equal or superior to those following castration.

(McCullagh, E. Perry, M.D. Cleveland, Ohio. *The Use of Sex Hormones in Cancer*. Cleveland Clinic Quarterly, Vol. 16 No. 1, p. 21 January 1949)

Haddow, A. Influence of Certain Polycyclic Hydrocarbons on Growth of Jensen Rat Sarcoma. *Nature* 136 808-809 November, 1935)

Book Reviews and Notices

SYMPOSIUM DE HEMATOLOGIA Y HEMOTERAPIA-1948, by J Guasch, A Ralchs, C Trincão, R Sarinajach, pp 522, Editorial "Miguel Servet," BARCELONA-MADRID, 1949, 22 x 16 cm

The symposium consists of seven articles. Every article has a summary in English.

The first one is entitled "*Penicillin in the treatment of the malignant neutropenias, simple and combined*". It reviews a series of 111 cases (85 from the literature and 16 authors') treated with penicillin. To combat sepsis responsible mostly for the fatal termination, in addition to the customary agents stimulating leucopoiesis, the authors advocate early and prolonged administration of large doses of penicillin (1 to 6 lacs units daily, intramuscularly). The second one "*Treatment of Kala-azar by splenectomy*" should be of great interest to us in this country. In a series of 38 cases of Kala-azar submitted to this surgical procedure, there were 5 operative deaths, 27 were declared as cured and in 6 the disease progressed to a fatal termination. Though the author has observed a cure in cases treated solely by splenectomy he advises this form of therapy only in those cases of Kala-azar which are resistant to specific chemotherapy by antimony compounds. Splenectomy removes the largest reservoir of the parasites in the body, and, what is more, by abolishing splenic hyperfunction corrects the haematologic abnormalities. The third article is on "*Constitutional elliptocytosis*". The authors conclude that elliptocytosis is familial and is inherited as a simple Mendelian dominant unrelated to race or sex. They studied in detail the blood pictures in a female camel and a male lama and compared the findings with those in the humans showing elliptocytosis. They remark that in the former the changes in the red cells are uniform and complete, while, in the latter, they are variable and incomplete. "*Leukaemia and pregnancy*" is a report of two cases of myelogenous leukaemia treated by irradiation. Both the patients had normal deliveries and the children were born healthy. "*Blood picture in clinical allergy*" is a study of the antigens and the antibodies concerned together with the chemical and cytological alterations in blood with special reference to hay fever and serum-sickness. "*Note on the distribution of the Rh factor in Spain*" gives the results of typing 400 individuals, 360 were Rh+ and 40 Rh—. The frequency of the Rh—negatives among the different races in that country is discussed in detail. The last article is on "*Therapeutics by the bone marrow way*". It deals at length with the local and general reactions produced by administration of varying volumes of fluids by the marrow route. An interesting observation of the authors is that in children administration of citrated blood plasma or serum by this route is less liable to produce reactions than in adults. The indications and contra-indications for the use of this route for therapeutic purposes are discussed in detail and the technique used by the authors described.

Every section is copiously illustrated with tables, charts and photomicrographs. A few of the last are not reproduced satisfactorily. An extensive bibliography is provided at the end of every article. Y M B

INDIAN HEART JOURNAL Vol 1 No 1, January 1949, Edited by B. B. Roy with the assistance of an All India Editorial Board for the Cardiological Society of India, 67, Dharmatala Street, CALCUTTA 13. Annual Subscription, Inland Rs 7/8/- Foreign 15s or \$3.00, post free, 25 x 17 cm.

There are many misconceptions about the prevalence of cardiovascular disease in India. Very little definite is known, though there

are many 'opinions' and 'experiences,' about the involvement of cardiovascular disease in a great many of tropical diseases and deficiencies. There is a vast field for physiological and pathological study of cardiovascular diseases as they occur in different parts of India, and it is in fitness of things that physicians interested in this study should join together in a society to exchange ideas and to develop their speciality. The cardiological society of India is a most welcome association and it is gratifying to note that the society has transformed their bulletin in a full-fledged *Indian Heart Journal*, the January issue of which publishes four original articles and two case reports of high scientific value. If this high standard of the first number is maintained, we are sure, the journal will meet a long-felt need of many physicians in India interested in the problems of circulation. We offer our congratulations and good wishes for the success of the new society and its journal.

THE CONQUEST OF TUBERCULOSIS by A. T. W. Simeons, M.D., Calcutta, Thacker Spink & Co., (Pp. xi, 75, Rs. 2/-) 1949

This booklet is meant for a patient suffering from pulmonary tuberculosis and tells him what *he* should do to conquer *his* disease. The title will not help some ambitious politician or a health minister to find in it a weapon with which he may ride his hobby-horse and enter the Realm of Medicine as a conquering hero!

Dr. Simeon's book is written in a homely and direct language of a physician talking to his patient, imparting his *faith*, *optimism*, and *enthusiasm* to a depressed victim who sees only a bleak future in front of him. There is much dogmatism and overstatement, but perhaps it is needed to arouse the enthusiasm of the patient. Dr. Simeons is concerned with the large number of cases of pulmonary tuberculosis for whom it is not possible to provide institutional treatment and pleads that it is possible to treat them in their own homes with equally good results if they are willing to take the trouble for about a year to get well. His technique is to institute a regime of (1) *voluntary immobilization* for six to eight months, (2) partial invalidism for another four to six months, and (3) rehabilitation for two to four months. The cases, in his opinion, most suitable for home treatment with 'voluntary immobilization' are (a) all early unilateral cases which are suitable for artificial pneumothorax treatment, (b) bilateral cases where pneumothorax treatment is not wholly satisfactory, and (c) all cases of, even advanced, bilateral tuberculosis where other treatment is not possible. Three types of clinical tuberculosis (1) the galloping type, (2) the general miliary haematogenous dissemination type, and (3) the old, indolent cavity-type, do not respond to this form of therapy.

Dr. Simeon's thesis boils down to (a) *absolute rest* at first and later, partial rest to allow natural healing processes a full scope, (b) *suralimentation* to supply energy, and (c) doubtful value of climate and environment in the control of tuberculosis. Rest is perhaps the most widely prescribed remedy in clinical medicine for a variety of diseases and one thinks of the emphasis laid on it by Hilton and Hugh Owen Thomas with their cry of "*Rest, rest, and yet more rest*." Still we know very little about the physiology of bed-rest and its value in the restoration of health. Recently there has arisen a cry against its indiscriminate use after surgical operations, after acute diseases, and in chronic, and even acute, heart disease. There is no scientific assess-

ment of its value in chronic diseases such as pulmonary tuberculosis. Bray has recently advanced the view that few patients with small and symptomless lesions benefit from rest, (*Amcr Rev Tuberc* 1945, 52, 483). He observed 67 subjects with early lesions who were allowed to live normal lives, there was a favourable response in 57, doubtful in 2, and unfavourable in 8. These results are similar to those claimed by Amberson, (*J Amcr Med Ass*, 1937, 109, 1949), who treated minimal cases with bed rest. Bray also studied 860 patients with incipient disease, 97 of whom had had approximately four months of strict bed rest before admission to a sanatorium, while the remainder had not. Subsequently all patients were allowed to live normal lives in the sanatorium. The course of events was similar in the two groups. Rest is useful in active cases with symptoms, the control of which should guide the duration and degree of rest.

'Food food, and yet more food' reminds one the old days of pounds of raw beef and mutton, and gallons of milk and codliver oil. While over feeding the patient, is it possible to feed the bacillus also? May not one starve the bacillus out by some special technique? We know so little about the 'nutrition' of the tubercle bacillus in the human body that it is dangerous to be dogmatic.

As regards the *climate*, Fowler, after fifty years of sending patients to South Africa, Egypt, and Switzerland, came to the conclusion, that "it is possible to cure a *wise* patient suffering from pulmonary tuberculosis *anywhere*, a *foolish* patient, *nowhere*". One feels that even after some 75 years of intensive work, we can do little to alter the natural course of pulmonary tuberculosis, mild and moderate cases do well, advanced cases go their own sweet way, we do not know when a mild case will suddenly become advanced, and we can rarely prevent the transformation. All our efforts are mere scratches on the surface of the vast problem.

Dr Simeon's book may be recommended to every sufferer from pulmonary tuberculosis and to physicians who have to deal with tuberculosis. There is much sound commonsense advice in it for all.

Our Problems a forum for discussion

REMARKS ON RURAL MEDICAL SERVICE

by

A T W SIMEONS, M D

Let us no longer speak of rural medical relief. The word relief has a temporary flavour about it which is not appropriate. What we are looking for is a *SERVICE* to be planned, initiated, developed and expanded until the whole wide land is covered with a permanent network of medical services of reasonable mesh.

The problem is gigantic. It goes deep down into the roots of the people, their hearts, their lives and their faiths. It also touches the very foundations of medicine, modern, scientific medicine. It is no use tinkering with such a problem which will turn the edge of little schemes however happily reasoned. A few mobile units, some cottage hospitals, bribing or forcing young graduates to work in rural areas are surely

little more than ill-tempered and impatient scratches on an unyielding surface

The administrative, the financial and the deeper intrinsic aspects of the problem, discouragingly formidable in themselves, are further magnified by certain set ideas, fixed ways of thinking, never questioned notions into which a critical investigation might be worthwhile. A little iconoclasm might help to clear away some obstacles in the path of evolving a satisfactory rural medical service.

Let us scrutinize a few basic conceptions which appear to have been readily, perhaps all too readily, accepted by our planners.

A policy which has been, I think, generally accepted without question, even in that masterly plan laid down in the Blore Committee's report, is a centrifugal spread from the largest city centres to better hospitals in district centres and from there into smaller hospitals in smaller townships finally branching into numerous smallest hospitals in strictly rural market centres. On closer examination it seems questionable whether this centrifugal policy is the best possible solution, whether it is economical, efficient and really suited to the existing conditions in this country. It is certainly not the way things have developed in other countries that have already advanced further than we.

It is generally true that the administrative and clinical efficiency of a hospital increases with its size. To run a modern hospital providing only the barest minimum of essential specialists and technical facilities for medicine, surgery, midwifery, E N T, ophthalmology, dentistry, pathology and radiology with less than about 500 occupied beds is fantastically wasteful and expensive. Yet any institution not providing all these services is not worthy of the name of a modern hospital. It becomes a place where a sort of mass general practice is performed. Where the harassed medical staff remain dilettanti in every branch and can at best offer third rate service. A rural diabetes, caesarean, glaucoma, carcinoma of the larynx or a ruptured appendix does not differ from its urban counterpart and the rural population has a right to expect Government to provide facilities of which the best are only just good enough. We must resist slipping into that unfortunate analogy that the primitive and backward villager and his ailments can get along for the present with primitive and backward medicine such as he must get in anything but the largest hospitals. Instead of using such funds as may be available for bringing hospitals into the villages it would seem more rational to concentrate on getting the villager into the hospital that can deal expertly with his case. In other words we should plan for a centripetal development.

We should begin not by building new hospitals but by bringing existing ones up to a really modern standard and provide more accommodation. Telegraph wires and fleets of ambulances will far more effectively bring modern medicine into rural areas than the establishment of small so called hospitals which will always be little more than a caricature of what a hospital should be. Wires and transport also cost far less, conserve our limited medical manpower and offer the best of our young graduates a splendid opportunity to spend more years of valuable schooling under specialists in really first class institutions before they venture out on their own into the scientifically bleak desert of rural or even suburban practice.

There never will be such a thing as a rural hospital. It is a contradiction in terms. What we need in the country is the country doctor, not the hospital. Without a wire and an ambulance the country doctor is terribly handicapped and can never develop into the magnificent role he plays in other countries. There he knows his limitations but they do not hamper him because he also knows that where his skill ends there the city hospital is ready at a moment's notice at any time of the day or night to despatch a fast ambulance, welcome and admit his patient and carry on where he left off. It is important that he has absolute confidence in the kindness with which his patient, a stranger in the vastness of the city, is received. He must be sure that the patient when he returns will be full of praise about the treatment he received particularly from the hospital menials otherwise the country doctor's authority in his villages is rapidly undermined. Hospital administration must always remain fully aware of the fact that a word of urban cheek handed by a bumptious wardboy to a frightened peasant can be a vicious blow to the professional standing of a country doctor. This most important psychological factor has perhaps been most fully appreciated in our big mission hospitals and accounts largely for their success.

The country doctor must be certain that no patient he refers for admission will ever be dealt with in an impatient out-patient department and refused admission. That, too, shockingly undermines his authority. City hospitals must accept the responsibility for referred patients from rural areas until they can be returned to their village or are able to make their own arrangements. They should never be summarily turned out into the street and must always be referred back to their doctor with a kindly and preferably personally worded report just as a consultant would do in the case of a referring general practitioner.

How can we build up a cadre of sound, thriving, satisfied and generally good country doctors? The present method of scattering young graduates far and wide over the country has not so far achieved nor can it ever achieve this object. Here are the reasons.

Sending one of our excellently trained young graduates into a rural area is just as if we would train a young ground engineer in a modern plane factory and then hand him a spanner and an oilcan and send him off single-handed into the jungle to repair a plane that has crashed there. Obviously a foolish waste of time, money and energy and a most humiliating experience for a promising and enthusiastic engineer, particularly as the old and experienced pilot sitting next to the crash is in a better position to handle his plane than the young specialist deprived of his tools and, of course, mumbles no words in saying so.

Let us not be impatient with the illiterate rustic unprepared to welcome a half-fledged doctor, and such is a raw graduate, into his compact society and with his unwillingness to share the intimacies of disease and childbirth with an outsider who to him is but a city slicker.

Let us on the other hand not be too harsh in condemning the young graduate who is still dreaming lovely dreams of degrees, research, eminence and riches for hesitating to plunge into the rural primitivity and hostility in which he is bound to flounder.

It is a fallacy to suppose that sending a young graduate into a rural area is going to benefit anyone. It will make the young doctor country for the rest of his life and it will convince the vil

modern medicine is a fraud and a failure The old village medicineman's authority will shine brighter than ever

Perhaps a most eminent physician after years of hospital work, though deprived of his technical paraphernalia, can do good healing in a village His vast experience would help him to get along where the newly ordained doctor would be hopelessly at sea

Paradoxically our young doctors are far too highly trained to work under village conditions until many, many years of experience enables them to adjust themselves to the country doctor's art and skill Yet it would be disastrous to put the curriculum into reverse and start training students for rural primitivity Not only would this be scientifically absurd and educationally disgraceful, it would also fail to achieve the desired result because it would still not enhance the young doctor's authority

This question of authority is of great importance in rural practice, in fact I am tempted to put it before professional skill because in the village skill without authority is utterly useless, nor can the young doctor, handicapped as he is from the outset, build up that authority unless he is very particularly gifted and exceptionally lucky The authority must be there from the beginning

Modern medicine is rapidly veering round to the psychosomatic approach in the etiology and the treatment of a host of diseases—more are coming into this purview almost daily Psychosomatic therapy is unthinkable without a solid foundation of authority Furthermore in the rural health services of the future, as I envisage them, the country doctor's recommendation to seek relief in a hospital must be indisputable It must be taken for granted that what the doctor says goes without the need for cross-checking by pundits and elders The responsibility must be placed upon and gladly accepted by the trusted doctor not by the family of the patient That requires the priestlike authority which elsewhere the country doctor almost invariably enjoys

What can our Government, so eager to cope with rural medical needs, do about it? In my opinion the first and immediately possible step is the establishment of rural subdispensaries in outlying areas on the lines I have worked out for the Kolhapur scheme This will establish confidence in modern scientific drugs and methods The second step is a long range policy of coaxing into existence a cadre of real country doctors

A possible way of doing this is as follows —successful elderly experienced, ethically and professionally unimpeachable, private rural practitioners of good standing should be encouraged to take in young graduates as assistants Both might be subsidised by Government until the mutual advantage of such a relationship is generally appreciated The combination of experience with modern technical skill should prove very satisfactory

The routine use of a microscope by private rural practitioners would do more than any other single measure to raise the standard of rural diagnosis and therapy No graduate should therefore be allowed to qualify for such a post unless he has proved his competence and willingness to do simple laboratory routine examinations of blood and excreta Let Government supply the instrument and recover some of the cost by a deduction from the subsidy The extent to which the microscope is made use of should be checked from time to time as also its care

The assistant should receive no fees for the first year, thereafter he might be entitled to a small percentage from such cases as he treats alone but under no circumstances may he practice on his own. The relation must remain an apprenticeship not a partnership for several years. Then when the assistant has become wellknown as having been trained by a doctor who already enjoys the population's confidence (his University degrees count for little in the village) he can eventually set himself up as an independent practitioner on the outskirts of his master's territory where he still enjoys the nimbus of the latter's authority.

It is of course most important that allocations are made according to the candidate's wish to be among people with whose language, way of life and nutrition he is familiar. The master too should be allowed to choose from possible candidates provided there is a check on nepotism. Moreover it would be necessary, as long as Government finds it useful to subsidise the scheme, to employ a carefully chosen inspector who should be a troubleshooting friendly councillor not a prying official, hidebound in regulations but say a sympathetic retired District Civil Surgeon.

I have met many private country practitioners whom I would consider admirably suited to act as Masters in this scheme, who would welcome relief from overwork, a microscope with someone who knows how to use it and a young breath of modern University teaching. I also know of some who would not be suitable. District Civil Surgeons can under no circumstances take over this role because they are liable to transfer and work as Government servants not as private practitioners.

Summing up I envisage three lines of approach to the problems on rural medical service —

(1) Enlargement of existing central hospitals, making them more "hospitable." An efficient ambulance service. Copper wire subsidised out of the Medical Budget if too uneconomical for the postal authorities.

(2) Immediate establishment of Rural Subdispensaries.

(3) Coaching real Country Doctors of a good type.

Notes on New Drugs

CHLOROMYCETIN

Chloromycetin (chloramphenicol, Parke Davis) is a pure, crystalline substance having specific antibiotic activity. This new antibiotic, obtained from cultures of the species *Streptomyces venezuelæ*, can also be prepared synthetically. Chloromycetin has been found to be effective against an impressive range of micro-organisms. Enteric infections, notably typhoid fever and other salmonella infections, bacillary, urinary infections and diseases in which the rickettsias are etiologic factors, are among the conditions which yield to Chloromycetin therapy. Experimental studies among other bacterial, rickettsial, and viral infections, including atypical pneumonia, psittacosis and lymphogranuloma venereum, indicate the possibility of adapting these findings to clinical treatment.

Dosage and Administration

Length of treatment is variable and is dependent on the character of the infection. For example, in treatment of scrub typhus a total dosage of 5 to 6 Gm. is necessary, and this amount should be given over the first twelve to eighteen hours. In contrast, the response of typhoid fever to Chloromycetin is not so abrupt and treatment should be continued for at least eight days, 3 to 6 Gm. should be given the first day and a total of 18 Gm. or more during the period of therapy. Details on therapy are given below.

The use of smaller doses increases the possibility of relapse. Optimal dosage given at intervals around the clock is necessary to assure maximum effectiveness.

Undulant Fever

The dosage recommended in treatment of this disease, is the initial administration of 60 mg per Kg of bodyweight and 0.25 Gm every three hours thereafter for at least seven days of normal temperature. Chloromycetin would be expected to exert some beneficial effect in the chronic disease, but treatment will probably have to be prolonged. Therapeutic effectiveness in the chronic state may be difficult to evaluate.

Bacillary Urinary Infections

The effect of Chloromycetin on bacillary infections of the urinary tract has been studied to a limited extent. While it is controversial as to whether bacilli are primary or secondary invaders, it does not seem to alter the clinical experience as to incidence, since urinary tract infections continue to occur in appreciable numbers.

In view of the favourable effect of Chloromycetin on the colon group of organisms demonstrated in the laboratory, the drug was a logical choice for clinical trial. In a series of 25 patients, showing various types of infection it was found that the urine became free of bacteria in one to three days when a dosage of 2 to 3 Gm daily (divided into two to four parts daily) was given orally.

Administration of Chloromycetin should be continued with 0.25 Gm three to four times daily for five to seven days after the urine is cleared of the principal invader, or until operative procedures have insured eradication of the focus.

Primary Atypical Pneumonia

The successful use of Chloromycetin in a few cases of primary atypical pneumonia suggests that it may eventually be found to have a favourable therapeutic action in this disease. Trial dosage was 0.5 Gm every two or three hours until 3 grams had been given, then 0.5 Gm four times daily. Temperature may become normal in thirty-six to forty-eight hours. Treatment should probably be continued for three to five days after the afebrile period in order to prevent relapse.

Typhoid Fever

Patients in Kuala Lumpur were given 50 mg per Kg of bodyweight initially. Then 0.25 Gm was given every two hours until temperature returned to normal and the same dose then repeated at three to four-hour intervals during the following five days. Total dosage averaged 19.1 Gm per patient given in a period averaging 8.1 days. No evidence of toxicity was noted clinically. Additional clinical experience with Chloromycetin in treatment of typhoid fever has confirmed the effectiveness of the drug in this disease, hence the above dosage is recommended.

Typhus Fever

Clinical study of Chloromycetin was initiated by Payne, Knaudt, and Palacios. Preliminary results of the work of these investigators in Bolivia were reported before the La Paz Medical Society and offered confirmation to the encouraging results previously found experimentally. Both oral and intravenous routes of administration were employed, and resulted in the recovery of 22 epidemic typhus patients treated with Chloromycetin who were subjected to an adequate follow-up of several months.

No toxic reactions or signs of intolerance were observed in this series and blood counts did not vary outside the limits of error for field estimation. It is recommended that the initial dose of approximately 60 mg per Kg of bodyweight be followed by 0.25 Gm (one Kapseal) every three hours until the patient becomes afebrile. Young children may require slightly greater amounts than those determined by proportional weight dose ratio.

Scrub Typhus

All treated patients received initial doses of 50 mg Chloromycetin per Kg of bodyweight followed by 0.2 to 0.3 Gm every two or four hours. At first treatment was continued for at least twelve days following onset of symptoms with a total dosage of 8 to 15.5 Gm. Duration of treatment was gradually reduced and the last 7 patients received a total of 6 Gm within a single 24-hour period. It is perhaps significant as a guide to future trends that patients under the short regime fared as well as those receiving more extended therapy.

Present recommended therapy is an initial dose of 60 mg per Kg of bodyweight, followed by 0.25 Gm (one Kapseal) every three hours for seven doses or until the temperature becomes normal.

Package Information

Chloromycetin is supplied in Knpsens (No 370), each containing 0.25 Gm (Parke Davis and Co Bombay)

THE INTERNATIONAL JOURNAL OF SEXOLOGY

The pre war quarterly *Marriage Hygiene* has now been reorganised under the title, *The International Journal of Sexology*. Sixteen regional editors have been appointed for the main geographical areas of the world. Unfortunately nil the contributions published so far have been from other countries. As the editorial board is anxious that Eastern and especially Indian view points should also be represented, articles, notes and comments are solicited. These may be submitted to the Editor in Chief, The International Journal of Sexology, Whiteway Building, Bombay—1

Reflections and Aphorisms

Four Principles of Medical Practice

"Medicine, perhaps more than any other branch of learning, is dependent on and intimately influenced by many essential and inter related principles. The first principle is, of course, the *science of medicine*, which has its origin in many roots. Proficiency in the science of medicine is a pre requisite in the development of an accomplished physician. The second principle, which is largely the outgrowth of innate endowment and experience, is the *art of medicine*. It comprises such factors as patience, understanding, compassion, tact and other finer sensibilities of humanity. The third principle concerns the *ethics of medicine* and embodies such qualities as honesty, sincerity of purpose, and a highly developed professional conduct. Without the possession of a superior ethical sense both in the science and art of medical practice become inadequate. Finally, the *culture of medicine*, a most important yet frequently neglected principle, completes the comprehensive professional personality. These four principles must be so carefully interwoven that a uniform professional texture is created in which one constituent does not predominate at the expense of the others."

F A WILLIUS & T J DRY

*

Subjective v. Objective Findings

"One of the defects of medical instruction leads to a deficiency which is commonly observed in students, house officers, practitioners, and even in teachers of clinical medicine. This is an inadequate appreciation of the importance of the subjective aspects of disease. The modern medical school is often unjustly accused of an over emphasis on laboratory methods of diagnosis. The importance of these methods and of the thorough physical examination *cannot* be overemphasised. However, in our eagerness to teach these *objective* and relatively new methods of analysis, there is a tendency to forsake our heritage from Hippocrates and Sydenham and to under-emphasize the older method of *subjective analysis*, i.e., the study of the patient's story of his complaints. Attending physicians, making hospital visits, are too ready to accept the history as obtained by a student, who has been inadequately trained for this important task because we have not taught him properly. We teachers know—but somehow we fail to convey it to our students—that in many patients the history is the most important diagnostic procedure and that often more skill, imagination, and ingenuity are required in evaluating the story than in making the physical examination, studying a blood smear, or interpreting a roentgenogram."

*

Physician and Society

"The physician occupies a special position in society in that he is the only person who combines training in the scientific method with occasion for contact with large numbers of the general public. This opportunity places an obligation upon him to try to set an example in objective thinking. He therefore should attempt to approach

those problems—whether political, governmental or economic—which involve society as a whole with that unprejudiced scientific attitude which he utilises in approaching the problems of the individual patient. In a world when the answers to many of the important questions confronting human society are being sought on an emotional rather than on a rational basis, the physician can render a great service if he will himself learn—and thereby teach others—that objective thought must supplant subjective feeling if the problems confronting mankind are to be wisely solved.”

Charm of Medicine

“Perhaps the greatest charm of medicine as a profession is the variety of facilities for happy work which it offers to men of the most diverse talents and interests. One man prefers the laboratory, another the library, a third the operating table and still another the consulting room. For the large majority of us, who are primarily interested in the sick patient, an exclusive devotion to books and laboratories leads to discontent and to Faust’s complaint

*‘I’ve studied now philosophy
And jurisprudence, medicine,—
And even alas! theology,—
From end to end, with labour keen
And here, poor fool! with all my lore
I stand, no wiser than before’*

The opposite extreme—becoming so interested in patients that reading and laboratory work are neglected—is a disastrous error and rapidly leads first to stagnation and then to retrogression. In my opinion, the greatest satisfaction comes from a judicious blending of the various types of work.”

T R HARRISON

Original Contributions

"ON THE EXPERIMENTAL TRANSMISSION OF RAT LEPROSY IN THE MOUSE WITH THE CULTURE OF MYCOBACTERIUM STEFANSKI ISOLATED BY SYMBIOSIS"

by

R ROW, M D (Lond) D Sc (Lond)

From the Department of Pathology, P G Sindhane Hospital, BOMBAY

Before outlining the experiments of the present memoir a summary of a previous communication (October 1948) on the subject of symbiotic culture may be of interest. There,¹ the author was able to confirm all his earlier findings by repeating his preliminary experiments of 1945-1946. He feels convinced that leprosy material when symbiosed with culture of growing protozoan e.g., *Leishmania*, enabled him to isolate the microorganism in culture. In the same communication, he also demonstrated that it was equally possible to isolate in culture the acid-fast microbes by a similar treatment of leprosy material in symbiosis with the culture of *Mycobacterium tuberculosis*. In short, he proved that by symbiosis whether with (1) a growing protozoal (*Leishmania*) or (2) *Mycobacterial* (tubercle) culture, leprosy material yielded a pure culture and subcultures.

Further, it may, perhaps, be useful to add that in analysing the several factors concerned in successfully isolating the mycobacteria, it is found essential to start with a fragment of leprosy itself instead of a material containing the bacilli only, so as to enable and ensure the preliminary proliferation of the microbes in the leprosy tissue itself, (much in the same way as it takes place in the infected progressive lesion *in vivo*), and thus prepare it for subsequent proliferation in the culture medium employed. The symbiosis played only a secondary role, however helpful, because it was found possible to obtain isolated colonies of acid-fast microbes on a glycerinated potato even before proceeding to symbiosis.

Briefly, by the technique employed both the *Mycobacterium leprae* and *Mycobacterium stefanski* were isolated and maintained in subcultures. These have been fully depicted and described (Figs 1 & 2 *Indian Physician*, 1948, page 257).

In attempting to study the biological and other characters of these subcultures, it was felt that, to begin with, it was best to put them to the crucial test of identification, *viz*, by animal inoculation experiments.

The present note deals only with *Mycobacterium stefanski*, because we have at our disposal an animal like the mouse to whom the microbe is pathogenic. It may be stated at once that as a result of such an experimental inoculation with the isolated culture, the author has been lucky in being able to transmit rat leprosy to the mouse for the first time. He has, therefore, ventured to feel that the result deserves to be recorded and this is done here at least in its own interest, with the full knowledge that the result recorded is the outcome of one single experiment.

Details of the Experiment

29-12-47

The infecting material and its preparation. — A mouse was inoculated intraperitoneally with rat-leprosy material on 29-12-47.

7-5-48

When killed on 7-5-48, it was found fully infected. Post-mortem the liver and spleen (which was enormously enlarged and friable) appeared smooth on the surface and both these organs were found studded all through uniformly with minute pin-head granulomata which were apparent on the surface even to the naked eye. A smear of the cut surface of the spleen showed microscopically a large number of acid-fast long bacilli, and a great many globi scattered amidst the blood corpuscles and cells of the spleen.

Symbiosis with the Culture of Mycobacterium Tuberculosis — The apparatus used here consists of an Ehrlynmyer flask of 50 c.c. into which is introduced a L3 Chamberland filter bougie, the flask is filled to the depth of about 3 cm. with the glycerinated nutrient fluid (Sauton) and the whole is sterilised after properly fitting it with cotton wool plug. Vide Fig. IV of Ref (1).

7-5-48

A small fragment of the infected spleen was crushed in 2 c.c. of normal saline and introduced into L3 candle in the experimental flask, at the same time a drop or two of suspension of a loopful of three weeks old *Mycobacterium tubercle* culture (on glycerinated potato) in 10 c.c. of normal saline was carefully instilled into the Sauton nutrient fluid in the flask—outside the L3 candle, the flask was incubated at 37°C.

21-5-48

The contents of filter candle when examined showed a few acid-fast bacilli but these were shorter than the original ones and were seen scattered in the midst of splenic cells, the tubercle culture was seen growing well in the fluid outside the candle as a well-marked film.

31-5-48

The contents of filter candle were again examined when it showed in the smear many fat acid-fast bacilli and several loosely packed globi all acid-fast, scattered amidst the altered splenic cells, the tubercle culture was seen as a vigorous growth in the form of a thick scum on the surface of nutrient Sauton fluid in the flask outside the filter candle, the fluid below the scum being clear and transparent.

10-6-48

The contents of the filter candle and the Sauton fluid outside it showed the same characters as on 31-5-48. A few drops were sucked up



Fig 1

Fig 2

Fig 3

Fig 1 *Myco stefanski*, third sub-culture of 10-11-48 from culture isolated on glycerinated potato

Infecting Material

(Obj 1/12 x Oc. 10)

Fig 2 Section of spleen of the mouse infected with above, 17 5-49

(Obj 1* x Oc. 10)

Fig 3 Smear of spleen of the infected mouse 17 5-49

(Obj 1/12* x Oc. 10)

All stained in Ziehl Neelson

June 1949

PLATE II
THE INDIAN PHYSICIAN

Patel N D —Ovarian Infantilism



Fig. 1, 2 and 3 (case 1)

Fig. 5 and 6 (case 2)

from the filter candle and planted on a glycerinated potato surface and the culture tube was incubated at 37°C

25-8-48

The extreme lower end of the potato surface showed a small thin smooth moist and translucent yellow patch which on examination reveals a pure culture of acid-fast coccobacilli, a subculture was made from this on a fresh glycerinated potato

15-10-48

A second subculture was made on a fresh potato and now the subculture was well established

10-11-48

It consists of a definite yellow film with smooth moist surface growing freely on the surface of glycerinated potato, *vide*, Fig III of Ref (1) It was made of pure acid fast coccobacilli and cocci (Plate I Fig 1)

10-11-48

Injection into the Mouse—A loopful scraped from the surface of potato culture 3 weeks old is suspended and rubbed into 10 c.c. of normal saline and of this 0.25 c.c. was introduced intraperitoneally into each of two mice

21-11-48

One of these mice died a few weeks later, probably accidentally and post-mortem showed no trace of the injected material in the peritoneum, liver or spleen

17-5-49

The second mouse, which appeared only a little wasted but otherwise well, was killed on 17-5-49 and post-mortem, the following features were recorded. On opening the peritoneum, no adhesions or other signs of peritonitis, recent or old could be detected, the liver appeared normal in size but pale with a smooth surface showing fine translucent pin-head granulomata even to the naked eye, the spleen was found enormously enlarged and was also smooth on the surface, not congested nor easily friable and to the naked eye revealed the same fine translucent granulomata scattered uniformly throughout as in the liver. A smear from the cut surface revealed enormous numbers of long fine acid-fast bacilli and innumerable globi of all sizes interspersed amidst blood corpuscles and cells of the splenic tissue (Fig 2 and 3, Plate I)

Conclusion—From the above it is evident that this experiment, though a solitary one and extending about 18 months, proves for the first time that the culture of *Mycobacterium stefanski*, isolated by symbiosis, is capable of transmitting the disease of rat leprosy in the mouse, and thus satisfying the most of Koch's postulates

A similar culture and subculture of *Mycobacterium leprae* has been isolated as a yellow film on glycerinated potato, *vide*, Fig, I Ref (1) Its investigation, for obvious reasons, is incomplete and left for a future study

The author desires to express his best thanks to his friend Dr. Pather the Resident and Associate Pathologist of this hospital for the great help he has rendered throughout this investigation during the last four years

REFERENCES

- (1) Row R (1948) Further observations on Symbiosis re *Mycobacteria* in Leprosy. The Indian Physician Vol VII No 10 Oct. p 255-258
- (2) IDRIE (1940) Isolation of *Mycobacterium leprae* in culture (Popular Lecture) Ibidem, Vol V No 4 April, p 75-81

ECTOPIC PREGNANCY

REPORT ON FOUR ADVANCED CASES

by

DR K M MASANI, M D (Lond), F R. C. S (Eng)
K E M Hospital, BOMBAY

It is generally stated that ectopic gestation was unknown before the time of Abu'l-Qasim uz zahwari (Albucassis) who lived about the middle of the eleventh century and described a case in his principal work, an encyclopaedia of medicine and surgery, entitled "*Altasrif*" Whether this was so and that this condition was altogether unknown to the ancient Hindus and Egyptians is not clear

The following is the description of the case

"I have seen a woman who, although a foetus had died in her womb, yet became pregnant again and had this second child also die in her A long time afterwards a swelling arose at the navel itself When this had been opened, matter flowed from it I was called in to see the case, and although I treated her for a long time, the wound could not be healed And so I applied strong medicaments of the utmost drawing power, with the result that a great many bones came out one after another, the sight of which greatly frightened me, since I knew that there were no bones in the abdomen Accordingly, after having carefully weighed all the facts and made thorough investigations, I recognized that they were the bones of the dead foetus, and so when I had now extracted more of them, I restored her to her former health, excepting only that she was always discharging something through the ulcer "

Since that time very little progress was made Cases of infected secondary abdominal gestation discharging pus and foetal bones through umbilicus, rectum, urinary bladder and vagina were reported till about the middle of the nineteenth century In the latter half of the nineteenth century the pathology and terminations of ectopic gestation were gradually clarified and the gravity of this condition was appreciated Abdominal surgery was in its infancy and gynaecologists of high repute hesitated to operate on ruptured ectopic pregnancy Parry remarking on this says, "The history of human injury and disease presents no condition parallel to this one However fatal the disorder, science and art have found some means of prolonging life or 'smoothing the stormy passage to the grave' But here is an accident which may happen to any wife in the most useful period of her existence, which good authorities have said is never cured, and for which, even in this age when science and art boast of such high attainments, no remedy, either medical or surgical, has been tried with a single success "

Playfair about the same time stated, "We must remember that the alternative is death and hence any operation which would afford the slightest hope of success would be perfectly justifiable I cannot, therefore, agree with those who hold that because the chances of success are so small this operation should not be tried, and I do not doubt that it will yet fall to the lot of some one by this means to snatch a patient

A Paper read before the 88th meeting of the Seth G S Medical College and K E M Hospital Staff Society held on 11th December with Dr J N Karande in the chair

from the jaws of death, and still further to extend the successes of abdominal surgery ”

Although Lawson Tait performed his first abdominal operation for ruptured ectopic pregnancy in 1883, he had met with a case in 1881 in which he had declined to open the abdomen and to his regret the patient died of further haemorrhage. Both the cases are described exactly as given by Lawson Tait. “In the summer of 1881 I was asked by Mr Hallwright to see with him in consultation a patient who had arrived by train from London in a condition of serious illness, that illness having been diagnosed by Mr Hallwright as probably haemorrhage into the peritoneal cavity from a ruptured tubal pregnancy. The patient was blanched and collapsed, the uterus was fixed by a doughy mass in the pelvis, and there was clearly a considerable amount of effusion in the peritoneum, but no distinct tumour could be felt above, and I agreed with Mr Hallwright as to the nature of the lesion. This gentleman made the bold suggestion that I should open the abdomen and remove the ruptured tube. The suggestion staggered me, and I am ashamed to have to say I did not receive it favourably. I saw the patient again, in consultation with Mr Hallwright and Dr James Johnson, and again I declined to act upon Mr Hallwright’s request and a further haemorrhage killed the patient. A post-mortem examination revealed the perfect accuracy of the diagnosis. I carefully injected the specimen which was removed, and I found that if I had tied the broad ligament and removed the ruptured tube I should have completely arrested the haemorrhage, and I now believe that had I done thus the patient’s life would have been saved.

“After the terrible lesson given to me by Mr Hallwright’s case I did not see another example of ruptured tubal pregnancy, or one which I suspected to be of that nature, till I was called to Wolverhampton, by Mr Speckmann on January 17, 1888. There could be no doubt as to the nature of the case, and Mr Speckmann was fully aware of it before I was summoned. The patient was clearly dying of haemorrhage, and I at once advised abdominal section. The foetus, about the twelfth week, was lying among masses of clot and coils of intestine, and to these latter the partially extruded placenta had obtained new attachments. These I cautiously separated and occasioned fast and copious bleeding at every point. I wasted much time in trying to stop this haemorrhage so that by the time the operation was finished my patient was practically dead. We got her to bed alive, and that is all that can be said. I thought much about this case for it was a bitter disappointment. I thought I should achieve a triumph and I had only a failure. But my conclusion was speedily arrived at that I had blundered—that the true method of operating in such a case was to separate the adhesions rapidly, regardless of bleeding, and make at once for the source of the haemorrhage, the broad ligament, tie it at its base, and then remove the ovum debris and clots at leisure ”

Advanced ectopic pregnancy may occur within the tube, ovary, or, secondarily, into the abdominal cavity.

Within the tube A few cases have been recorded where the ovum has continued its development in the tube without interruption to an advanced stage. Ampullary portion is the most frequent site of ectopic embedding of the ovum and, being the most distensible portion, advanced

development without interruption is most likely in this part of the tube. The tubal musculature undergoes hyperplasia and hypertrophy, but is in no way comparable to the uterine musculature. The enlarging tube soon contracts adhesions to other abdominal structures such as omentum and intestines, and a pseudo sac is formed outside the tube reinforcing and supporting the pelvis and partly above the pelvic brim. At term, 'false' labour occurs and the foetus dies following tumultuous movements. Occasionally, a living child has been delivered by abdominal operation.

Within the ovary Williams carefully studied all the reported cases of ovarian pregnancy upto 1906 and found that pregnancy had gone to full term in 11 out of 85 cases. He stated that in several of them a lithopaedion had formed. He was convinced that the case recorded by Gottschalk in 1898 and by Ludwig in 1896 had gone to full term. From his careful study he concluded that ovary could accommodate itself more readily than the tube to the growing pregnancy, although rupture at an early period was the most usual termination. When embedding occurred on the surface of the ovary, early rupture was the rule but when the ovum was embedded deeper, pregnancy could occasionally advance to full term.

Secondary intra-peritoneal abdominal pregnancy Ley tabulated abstracts of 100 cases from the literature in 1919. Cornell and Lash in 1938 collected 266 cases from the literature. Suter, Jacksonville and Wicher have reviewed 41 cases from literature between 1930 and 1945. Secondary abdominal pregnancy was met in patients as young as 15 and as old as 64, but the majority of cases occurred between the ages of 20 and 40.

Secondary abdominal pregnancy is likely to develop to an advanced stage if the development within the tube continues for some weeks before interruption. If early rupture occurs, the embryo is rapidly absorbed by an action of phagocytes as was shown by Leopold in 1881 on animals. For the development to continue the placental attachment must have been relatively intact. Formerly it was believed that the embryo could continue its development if it was extruded from the tube with its membrane intact, but at the present time this is not considered as an essential requirement for continued growth.

It is extremely doubtful if secondary implantation can occur after the placenta is fully formed as, by then, the erosive property of the chorionic villi has disappeared. Secondary abdominal pregnancy is then possible only if most of the placenta remains attached to the tube. Even when rupture has occurred during the first few weeks while the trophoblastic activity is still present, secondary attachment to surrounding structures must be difficult because (1) during separation of the ovum from its primary attachment it is surrounded by blood clot and direct contact of villi for secondary attachment to abdominal structures is absent, (2) the villi deprived of their nutrition from maternal tissues cannot remain active unless immediate reattachment can occur. It has been suggested that all the cases described as secondary abdominal pregnancy are in fact instances of primary abdominal pregnancy developing to an advanced stage without interruption.

When the attachment of the ovum is at the extreme fimbrial end, it is possible for the ovum to lie within the peritoneal cavity as develop-

ment continues without any rupture having occurred. Another possible way in which a tubo-abdominal pregnancy could result is when the foetus continues its growth in the tube, the muscular layer of which is so stretched and attenuated that the gestation sac is only separated from the peritoneal cavity by the peritoneal coat of the tube.

When the foetus escapes into the peritoneal cavity, either with its membranes intact or without them, there is the formation of a pseudo sac from organisation of blood poured out at the time of rupture. The sac is still further reinforced by a localising peritonitis around the sac outside which lie the coils of intestine, omentum and other abdominal structures.

Of the 266 cases collected by Cornell and Lash, 152 babies lived for 8 days or more, 118 died within 8 days, and the fate of 1 was not known.

Secondary extra-peritoneal abdominal pregnancy. Champion and Tessitore in 1938 reported 70 cases of intraligamentary pregnancy that had developed for over 7 months. They stated that upto the end of the last century only 30 cases had been recorded, the first being an account of autopsy findings by a German, Loschge, in 1816. It is generally assumed that this variety of ectopic pregnancy results from rupture of a tubal pregnancy into the broad ligament. They, however, state that certain conditions must be fulfilled to permit an ovisac to become secondarily implanted into the folds of the broad ligament.

(a) Implantation must have occurred in that part of the tube which was uncovered by peritoneum.

(b) The ovum must have ruptured early before the trophoblast had lost its power to ensure secondary nidation. When villi have been formed this action is naturally lost.

(c) The interval between the primary and the secondary implantations must have been short or else death of the foetus would have occurred.

(d) Accordingly to Frankel and Schenck, endometrial tissue is a pre-requisite to nidation.

Champion and Tessitore suggest an alternative explanation that an intraligamentary pregnancy results from implantation on the posterior layer of a primary abdominal or a primary or a secondary ovarian pregnancy. As a result of growth, the posterior layer of the broad ligament becomes thinned out and ruptured allowing further growth inside the broad ligament. This is often indicated at operation when after the removal of the ovum there is difficulty in peritonising the wound.

The growing ovum accommodates itself by stripping the anterior or the posterior layer of the broad ligament upto a certain level after which growth of the sac occurs without further stripping. The result of this is that although the sac was entirely outside the peritoneum it is not much more than in an intra-uterine pregnancy.

The placenta is usually *above the focus* and may get attached to the liver and other posterior abdominal structures.

Physical signs when pregnancy reaches to advanced stages. The gestation sac increases as in intra-uterine pregnancy. On inspection, foetal movements are very distinctly observed but, when placenta is

situated in the anterior wall of the gestation sac, movements may not be observed

Foetal parts are very easily felt and minor details of different parts of the foetus can be made out

On vaginal examination, the cervix is found to be firm and not soft as is the case during later months in intra-uterine pregnancy. The presenting part is not within the reach of the vaginal fingers and this arouses suspicion of abdominal pregnancy. On careful palpation, the uterus is found to be of small size and displaced forwards and laterally. Passage of an uterine sound to confirm diagnosis will reveal the small size and direction of the uterus felt by bimanual examination.

If the case has not been detected before 'false' labour has occurred then suspicion will be aroused by non-dilatation of the cervix and the presenting part remaining above the pelvis. The hardening of the uterus during pains is not observed during pains of 'false' labour. Vaginal bleeding occurs during 'false' labour and may be mistaken for 'show' occurring at the onset of labour in uterine pregnancy.

After the death of the foetus, liquor amni is absorbed, the foetal heart is not heard and the foetal movements are not felt. If it is retained in the abdominal cavity for a long time, the foetal parts cannot be felt and a cystic abdominal tumour of varying consistency is felt. At this time, X-ray of the cyst reveals remnants of foetal skeleton and irregular calcification.

If the foetal sac gets infected an abscess results which may open after some time at some place in the abdominal wall, the rectum, vagina, or the urinary bladder. A sinus remains for many years and, at intervals, foetal bones are discharged through it. The general condition of the patient also deteriorates due to low grade continued sepsis.

Treatment of Secondary Abdominal Pregnancy Treatment of secondary abdominal pregnancy presents many problems some of which have presented difficulties in the past. Secondary abdominal pregnancy may be intra-peritoneal or extra-peritoneal, the extra-peritoneal may be of anterior or posterior variety. Each of these presents problems regarding the best methods of evacuation. Another factor requiring attention is the optimum time for interference from the stand-point of both the mother and the child.

The best time to operate in the interest of the child is about the 38th week. If operation is undertaken before the eighth month, the foetus is very premature and not likely to survive. If, on the other hand, operation is delayed till full term, intra-peritoneal death either during the last two weeks or at the time of the beginning of the 'labour' or within 48 hours after the onset of 'labour' occurs in a good number of cases. It is concluded from the figures observed that the best time from the stand-point of the child is the 38th week.

Beck's findings were as follows. In 202 cases in which the period of gestation was from 28-40 weeks, 80 infants survived one month, 39.6%; in 80 cases in which the period was from 32-40 weeks, 38 infants survived one month, 47.5%, in 140 cases in which the period was from 36-40 weeks, 72 infants survived one month, 51.4%, and in 60 cases in which the period was from 36-38 weeks, 34 infants survived one month, 56.6%.

The child is frequently deformed or maldeveloped from pressure and there is difference of opinion regarding the wisdom of waiting till the 38th week. Cornell and Lash noted deformities in many of their cases. Their conclusion was that "while many of the deformities were corrected by treatment the high incidence of deformities should be considered before advising a patient to attempt to await term before submitting the operation."

From the stand-point of the mother the question is important, because if maternal risk is increased by waiting in the interests of the child till the 38th week, then the interests of the child should not be taken into consideration. The main disadvantages of waiting till the 38th week are rupture of the sac with sudden, diffuse hæmorrhage and infection of the gestation sac from the surrounding intestines. The advantage claimed for waiting is that as long as the foetus is alive and for some weeks after its death the placenta is 'quick' so that severe and uncontrollable bleeding may be encountered during its separation. Although the placental circulation may be arrested after the death of the foetus rendering the separation of the placenta easy, the risk of infection of the gestation sac is increased.

Beck has carefully analysed his cases from the point of operative mortality at different periods of gestation and his conclusions are. The danger from the operation itself increases as the pregnancy advances, until the last month is reached when it is less than at the previous time. An analysis of all the deaths shows the apparent reason for this diminished risk during the tenth month to be a lessened tendency towards hæmorrhage at that time. After the 38th week, 86.8% of the deaths were due to hæmorrhage, while almost twice as large a proportion, 65.3%, resulted from this cause when the operation was performed before the last two weeks.

The abdomen is opened by midline incision. As the sac is usually adherent to the anterior abdominal wall great care is necessary in opening the peritoneum. The sac is carefully separated by finger and blunt dissection until the foetus is reached. The foetus is then easily extracted. In a few cases, the placenta may be adherent to the anterior abdominal wall. In such cases the placenta will be cut into as the abdomen is opened and the bleeding can be controlled by clamps. After the foetus has been extracted, deliberate and careful exploration to find out the attachments of the placenta is necessary. In the majority of cases the placenta is attached to pelvic viscera or to the omentum, small intestines, anterior abdominal wall and rarely to other abdominal viscera.

If separation of the placenta is commenced before knowing its attachments and its chief blood supply, severe and uncontrollable bleeding may occur during separation and the operator is compelled to close the abdomen after packing the cavity with gauze. If separation is continued in spite of severe bleeding, the life of the patient is endangered. Cornell and Lash remark in this connection "In reading the case reports, it is surprising to note the number of surgeons who persist in attempting to remove the placenta in spite of the severe hæmorrhage. We believe that the mortality can be lowered greatly if one desists from interfering with the placental site when it becomes evident that hæmorrhage is uncontrollable."

In a few fortunate cases, the greater part of the placenta is still within the Fallopian tube and in such cases the tube forms a pedicle and salpingectomy is sufficient to control bleeding. In other cases, most of the placenta is attached to the back of the uterus and the broad ligament. In 236 cases collected by Cornell and Lash, the placenta was attached to the uterus in 67 cases and to the broad ligament in 57 cases. In such cases the problem is simplified if it is possible to control the bleeding from the ovarian artery before the separation of the placenta is begun. It is sometimes possible to amputate the uterus and remove it with the placenta attached to it. The operation is commenced by clamping and cutting the broad ligament of the opposite side, followed by amputation of the uterus at the internal os. After securing the uterine artery of the other side and, if possible, the ovarian artery at the pelvic brim, the placenta is peeled off without serious bleeding.

The treatment of placenta in those cases where its removal is difficult or almost impossible has been always a difficult problem. Formerly, when the placenta could not be removed, it was marsupialised by stitching the sac to the anterior abdominal wall. Drainage of the abdomen with the placenta left in was another method in use. Both these methods appear to be the worst methods as shown by statistical survey of Cornell and Lash, Beck and Mason. Mason in reviewing 69 cases from 1933-39 reported in the English literature records some interesting data.

TABLE

Treatment of Placenta	Recovered		Died	
	Uncomplicated	Complicated	Cases	Mortality %
No attempt at removal:				
(a) Abdomen closed without drainage or packing	8	4	0	0
(b) Placenta marsupialized, or abdomen drained or pack used	1	4	5	50
Placenta removed or unsuccessful attempts at removal				
(a) Abdomen closed without drainage or packing	1	1	0	36.3
(b) Placenta marsupialized, or abdomen drained or packed	0	5	4	
Placenta easily removed in entirety				
(a) Abdomen closed without drainage or packing	21	0	1	4.8
(b) Placenta site packed or abdomen drained	0	4	1	20
Placenta removed in entirety with difficulty				
(a) Abdomen closed without drainage or packing	0	2	1	22
(b) Placenta site packed, or abdomen drained	2	3	1	

Of the 56 patients who recovered 25 or 44.6% were those in whom the placenta was easily removed, and 17 or 30.3% were in patients in whom no attempt was made to remove the placenta.

Seven patients in these two groups died, but there was only one death among those patients in whom the abdomen was closed without packing or drainage, a mortality rate of 2%. There were 5 deaths among those patients (22) in whom no attempt was made to remove the placenta or a rate of 22.7%, but they were in those patients in whom the placenta was marsupialised or in whom drainage was employed. There was no recorded death among the patients in whom no attempt was made to remove the placenta and in whom the abdomen was closed without drainage.

Important conclusions arrived at from this survey are —

(1) There were no deaths in the group in which no attempt was made to remove the placenta and in which the abdomen was closed without drainage

(2) The greatest number of deaths of all the groups occurred in those in which no attempt was made to remove the placenta, but in which the placenta was marsupialised or in which drainage was employed

(3) The group in which the placenta was easily removed and in which no drainage was employed, the highest number and percentage of uncomplicated recoveries was recorded

Necrosis of the placenta is a physiologic process and it can be safely left in the abdomen without drainage. The convalescence in majority of the cases where the placenta had been left in situ and the abdomen closed without drainage was uneventful, but Nicodemus and Carrigg, Lull, and Pearson have each recorded a case of abdominal pregnancy requiring secondary removal of the placenta.

In the case reported by Nicodemus and Carrigg, the placenta was left behind as it was attached to the omentum, ileum, and ascending and transverse colons. Shortly after the first operation, the patient returned for loss of weight, appetite and rise of temperature. At operation, a large quantity of pus was drained off and the unabsorbed placenta was easily shelled off.

In the case reported by Lull, the placenta did not absorb and, two months after the first operation, the abdomen was again opened and part of a large hæmorrhagic cyst was removed but the rest was closely adherent to the intestine and was marsupialised and packed. The recovery was uneventful.

In Pearson's case, rust-coloured fluid was drained off three months after the first operation. The placenta was found to be attached to the posterior and superior wall of the uterus. A supra-cervical hysterectomy with bilateral-salpingo-oophorectomy and appendectomy was done. The abdomen was closed without drainage.

When the pregnancy is intra-ligamentary the problem of dealing with the placenta and the sac offers further difficulties. The placenta is situated usually above the ovaries in intra-ligamentary type. Due to the growth of the foetus, it is displaced more and more in an upward direction and hæmorrhage occurs into and around it. Due to the vicinity of the sigmoid colon in posterior variety, infection of the hæmatoma with the formation of pus is a likely complication. Adhesion of the placenta to extra-peritoneal viscera, such as the liver, may also take place during its progressively upward growth, and removal of the then gives rise to severe bleeding.

In anterior intra-ligamentary pregnancy, the floor of utero-vesicle pouch may be raised as high or above the umbilicus and the bladder is likely to be injured during the opening of the abdomen. In such cases, the whole operation can be performed extra-peritoneally. If the placenta is above the ovisac, it will necessarily be cut into before the foetus can be extracted. The placenta can then be peeled off and the cavity packed with gauze to arrest generalised oozing. If the placenta is situated below the ovisac its removal may be difficult.

In posterior intra-ligamentary pregnancy, the peritoneal cavity is opened and then a bulging mass is found arising from the posterior pelvic wall covered with posterior parietal peritoneum. The general peritoneal cavity is packed and the foetus with the blood clots is removed by incising the peritoneum over it. The treatment of the placenta, whether to be removed or left behind, will depend on its attachments and also on the presence or the absence of infection.

Four cases of Secondary Abdominal Pregnancy The special interest in presenting these four cases is that all the four are of different varieties, and different methods of diagnosis and treatment were necessitated in each type.

Case I—Dr Miss Daruwalla's case reported in G S M College Magazine of November 1940.

A Mahomedan woman, Para III, was admitted to the Dholkawalla Hospital on 11th December 1939. Her first was a normal full term delivery, her second was a Caesarean Section for disproportion done at the Nasik Mission Hospital 2½ years previously. The latter information she withheld until her readmission in January 1940. She gave a history of 8 months amenorrhoea, slight abdominal pain and vaginal bleeding.

On examination she was found to have ankylosis of the right hip and knee-joints, the result of a fall at the age of 8 years. The "fundus uteri" was three inches below the xiphisternum. The presentation was by the vertex and appeared to be engaging. The foetal heart was heard. Pelvic measurements, blood-pressure and urine were normal. Rectal examination revealed a soft cervix, slightly less than one finger dilated and the head palpable through the fornices. There was no vaginal bleeding.

On the third day of admission she complained of slight abdominal pain accompanied by slight vaginal bleeding, and on vaginal examination the cervix was found to admit one finger with difficulty and a blood clot was felt through it. On the fourth day she passed two small clots, the pain subsided and the foetal heart became rather indistinct. A rectal examination showed the cervix closed again. A medical induction was attempted without result. Soon after this she left the Hospital against medical advice.

She was re-admitted in January 1940 for slight vaginal bleeding and volunteered information about the previous Caesarean section. She was transferred to the Wadia Maternity Hospital where an x-ray was taken. The x-ray showed overlapping of the skull bones (Spalding's sign). Her blood picture showed slight secondary anaemia, her W B C count being 6,000. Urine showed a few pus cells. Medical induction was tried with no result and she started running a slight temperature which was thought due to toxic absorption from the dead foetus.

On the subsidence of temperature medical induction was again attempted with a negative result. On vaginal examination the cervix was found small and firm and continuous with a firm mass on the right side which was now thought to be the uterus and the abdominal tumour a gestation sac. A sound passed into the uterus passed towards the right for a depth of 4 inches. Hystero-salpingography showed a large and irregular shadow of the uterus, quite separate from the foetal head. The right Fallopian tube was visualised but not the left.

Laparotomy was performed under nitrous oxide and ether anaesthesia. The intact gestation sac was found lying in the peritoneal cavity, arising from the fundus of the uterus in the region of a ruptured Caesarean scar and adherent in parts to the intestine and omentum. The placenta was attached to the left postero-lateral surface of the uterus and the surrounding peritoneal surfaces. A comparatively well preserved foetus was removed from the sac, and the placenta was then separated from its adhesions. A subtotal hysterectomy was also necessary. Persistent oozing necessitated packing of the pelvis.

In spite of a post-operative transfusion of blood the patient died within 48 hours.

Case II—Dr. Miss Daruwalla's case reported before the Bombay Obst. and Gynaec. Society in 1942.

Mrs. S., aged 28, Hindu, Para III, presented herself for registration at a private maternity hospital on 12th January, 1942. She had had 2 previous normal deliveries which according to her were rather precipitate and at the last, which was 7 years previously, a manual removal of placenta had to be resorted to. This time she gave a history of six months amenorrhoea, during the first two months of which she had bleeding per vaginam which persisted for about 5 weeks accompanied by slight pain in the abdomen and then stopped spontaneously.

On examination, her general condition was good, B. P. 140/95 with a trace of albumin in the urine, pelvic measurements were normal. The foetus was presenting by the vertex and lying in position I. The fundus was 9 inches above the symphysis pubis. Nine days later the findings were the same except that the fundus was $\frac{1}{2}$ inch higher. At the third visit 15 days later she complained of attacks of abdominal pain. The fundus was now 10 inches above the symphysis. A sedative mixture was prescribed. At the fourth visit the presentation was thought to be a breech and two attempts at version were made before the error was discovered. Three weeks later she returned with severe pre-eclampsia. She was admitted and the following day she complained of loss of vision. She was given the usual treatment for pre-eclampsia and vision gradually improved and other signs cleared up.

It was decided to induce labour but on vaginal examination the cervix was found soft and high up anteriorly and the head was felt low down through the posterior fornix. Under anaesthesia two fingers were passed through the cervix into the uterine cavity which was found to be empty. The uterus which was anterior and to the left of the body of the foetus was about 8 months size. A diagnosis of advanced extra-uterine pregnancy was made.

At laparotomy in the N. W. M. Hospital under local infiltration anaesthesia supplemented with ethyl chloride, the uterus which was about 4 months size was found pushed to the left. It was surmounted

by a small fibroid. The left tube and the round ligament were normal. The right round ligament was also normal but the right tube traversed the top of the gestation sac and merged with it. The gestation sac was adherent to the top and right side of the uterus, and large venous sinuses were found coursing over it. A vertical incision was made through a non-vascular portion of the sac and the child removed easily. As much of the amnion as possible was removed and the opening closed by a purse-string suture, the placenta being left in situ. There was no bleeding after closure of the sac. Post-operatively 400 c.c. of fresh blood was transfused by the drip method. The child was a male, had no deformity and weighed 6 lbs 2 oz. It was pale and asphyxiated and died on the fourth day.

The patient was progressing well till about 20 hours after operation, when she suddenly collapsed and died within one hour.

At post-mortem it was found that the cause of death was haemorrhage into the sac from one of the ruptured placental sinuses. It appeared that the pregnancy had ruptured into the right broad ligament from the right tube. It had then enlarged upwards and to the left raising up the peritoneum of the pouch of Douglas and then burrowing between the two layers of the meso-sigmoid which was lying sessile over the left surface of the sac. The sac was adherent to both ureters especially, the right which was thickened, dilated and tortuous and looked like a coil of small intestine.

Case III — Advanced Pregnancy in a Rudimentary Horn. Mrs R. R., age 24, Hindu, Para II, with one full term normal delivery two years previously was seen by me when she was seven months pregnant. Nothing abnormal was detected. No vaginal examination was done and she was referred to the Wadia Maternity Hospital for registration for her confinement. She was admitted in July 1946 at the Wadia Maternity Hospital with a history of 8 months amenorrhoea and pains resembling labour pains. The pains subsided and she was discharged.

She was readmitted 3 months later with a history of 11 months amenorrhoea and labour pains. An x-ray at the time showed a macerated foetus. The pains again subsided and since she was running a temperature due to Filariasis for which she was being treated elsewhere she was discharged with instructions to return when pains started. No vaginal examination was done.

The patient did not report and was seen by me in January 1947 with history of 14 months amenorrhoea and irregular bouts of vaginal bleeding during the previous 3 months.

Abdominal examination revealed a mass arising from the pelvis and reaching up to the umbilicus. It had the shape of the uterus but did not undergo contractions. No foetal parts were palpable nor was the foetal heart heard. It was dull on percussion and not tender. Vaginal examination showed a parous cervix and a mass was felt arising out of the pelvis and indistinguishable from the uterus. Her blood-pressure, urine and blood picture were normal.

Diagnosis of secondary abdominal pregnancy was made.

At laparotomy the uterus was found unequally enlarged. On the left side the normal uterus communicated with the cervix. On the right side an accessory horn was discovered connected with the right Fallopian tube and round ligament. The horn was incised vertically and a

macerated foetus removed. Bleeding was slight. The redundant portion of the horn was removed with the placenta attached to it and the remaining portion sutured up. No communication between the horn and the cervical canal was discovered.

There was pyrexia for the first two days which responded to sulphadiazine therapy. Slight urinary tract infection was treated with "pyelopurin". She was discharged from Hospital on the twentieth day after the operation.

Case IV—Secondary Abdominal Pregnancy Dr Masani's case

Mrs C H, para II, first attended the O P D for ante natal examination on 27th January, 1948. She had one full term normal delivery 8 years previously and the child was living. She gave a history of 7 months amenorrhoea. At about the third month of pregnancy she had severe pain in the abdomen, vomiting and slight vaginal bleeding. The bleeding stopped in about 15 days but the vomiting continued until the sixth month. The pain still continued in a lessened form. On examination the foetus was found lying obliquely with the head in the left iliac fossa. The foetal heart was heard. External version was unsuccessful.

She was seen again on 10th February, 1948, when in view of the history and the apparent superficiality of the foetal parts an advanced extra-uterine pregnancy was suspected and she was admitted for investigation. A vaginal examination was made but was inconclusive. A hystero-graph was therefore done. It showed a slightly larger uterine cavity than normal. The tubes were not outlined, but, separate from the uterine shadow, was seen a normally developed apparently full-term foetus. The blood picture was normal.

On 20th February, 1948, at about 8 a.m. the pain in the abdomen became more severe and slight vaginal bleeding started. At about 10 a.m. a decidual cast was passed. The foetal heart sounds were still heard and she was prepared for an operation.

At laparotomy the gestation sac was seen to arise from the top of the right Fallopian tube and broad ligament. There were no other adhesions. The sac was opened and a normal full term living infant was removed. The placenta presented itself in the lower part of the abdominal incision and was found to arise from the right Fallopian tube and adjacent broad ligament. The right Fallopian tube along with part of the broad ligament with the attached placenta and membranes were removed.

During operation she was given 200 c.c. of glucose saline and post-operatively penicillin was given prophylactically.

Her convalescence was uneventful and both the mother and the child left the Hospital well on the 22nd post operative day.

Clinical Case Reports

OVARIAN INFANTILISM RESULTING FROM OVARIAN APLASIA OR AGENESIS

REPORT OF TWO CASES

by

N D PATEL, M.D (Lond), M.R.C.P (Lond), F.C.P.S

G S Medical College and K. E M Hospital, BOMBAY

Turner (1988) and Albright (1942) have described a new syndrome characterized by primary amenorrhoea, sexual infantilism, short stature, webbing of the neck, and cubitus valgus in the females, who excrete abnormally large amounts of urinary gonadotropins. Primary ovarian insufficiency due to congenitally aplastic or rudimentary ovaries is suggested as the cause of the syndrome. The main clinical, anatomical, and biological features of the syndrome are

- (1) Short stature of moderate degree and stocky build,~
- (2) Primary amenorrhoea,
- (3) Infantile genitalia and hypoplastic uterus, absence of breast development, and scanty or absent pubic and axillary hair,
- (4) Rudimentary or absent ovaries,
- (5) Hypophyseal gonadotropins excreted in excess in urine, subnormal urinary estrogens, and diminished 17-keto-steroids,
- (6) Delay in aging of bone, diffuse osteoporosis and vertebral chondrodystrophia,
- (7) A number of congenital abnormalities such as, webbing of the neck, scoliosis, cubitus valgus, syndactylism, coarctation of the aorta, absent upper lateral incisor teeth, etc are associated with the condition

Diagnosis—In making a clinical diagnosis of genetic ovarian insufficiency one may consider—*Age*—most of the cases published fall between the ages of 15 to 50. *Onset* is during school age, between 7 and 16. *Diagnosis* is only possible after the failure of menstruation but it is possible to suspect the disorder in childhood. *Stature* is between 130 to 145 cm (under 57 inches). *Build*—stocky and short. Dwarfism is supposed to be a genetic factor and not due to ovarian aplasia. The *chest* is barrel-shaped or shield-form with widely spaced nipples and increased anterioposterior diameter. *Sexual retardation* is shown in the absence of breast development, absent or scanty pubic and axillary hair, (scanty sexual hair growth is due to disturbance of suprarenal function and not due to ovarian aplasia), infantile external genitalia, and infantile or absent internal genitalia. There is *primary amenorrhoea*. *B P* readings are low but are not significant. *Other abnormalities*—Webbing or apparent shortening of the neck, cubitus valgus, coarctation of aorta and various forms of vascular and skeletal abnormalities may be present. The *bone age* shows retardation in a few cases, but most cases show normal development. *Osteoporosis* is present in some cases. *Visual field defects* have been recorded in a few cases. The *insulin tolerance test* is normal. The abnormalities present are as-

cribed to (1) a genetic factor, (2) an absence of the ovarian hormone, and (3) a diminished adreno cortical function

The clinical diagnosis is suggested in the presence of some of the above features, e.g., primary amenorrhoea, short stature, absent or scanty pubic and axillary hair, failure of mammary development, and some congenital abnormality. Biological tests for the estimation of urinary hypophyseal gonadotropins (increase), estrogens (low), and 17-ketosteroids (diminished) are necessary to make the diagnosis more certain. Absolute certainty is only possible after biopsy i.e., histological study of ovaries after laparotomy, disclosing their aplastic or rudimentary nature. This last examination is rarely necessary if the clinical examination is thorough and if there are laboratory facilities for biological study. The other causes of dwarfism such as pituitary infantilism, eunuchism, infantile myxedema, mongolism, achondroplasia, congenital heart disease, diabetes, rickets, renal disease, and malnutrition are easily diagnosed, except that there may be difficulty to differentiate the condition from *primary pituitary infantilism* where the following points of differentiation, taken from Del Castillo, will be found useful —

<i>Rudimentary ovaries</i>	<i>Hypophyseal dwarfism</i>
(1) Women of short stature	(1) Dwarfs
(2) Infantile mammary glands and genital organs	(2) The same
(3) Scanty development of pubic and axillary hair	(3) Lack of pubic and axillary hair
(4) Well nourished and strong	(4) Weak and easily tired
(5) Bone age some years retarded	(5) Very marked delay in bone age
(6) Late closure of the epiphyses	(6) Lack of closure of the epiphyses.
(7) Very frequently vertebral chondrodystrophia	(7) The same
(8) Follicle stimulating hormone increased in the urine	(8) Lack of follicle stimulating hormone
(9) 17-ketosteroids somewhat diminished	(9) 17 ketosteroids considerably diminished
(10) Normal insulin curve	(10) There is no response to insulinic hypoglycemia
(11) Congenital abnormalities, among them aortic coarctation and "Sphynx" neck	(11) Not observed
(12) Diffuse osteoporosis and early senility	(12) Not observed
(13) Normal sella turela	(13) Pathological modification may be observed
(14) Visual fields some functional alterations	(14) Abnormalities in the presence of a neoplastic lesion

Treatment — In the complete absence of ovarian hormones, the only rational treatment is estrogen substitution, and there is no question of stimulation by anterior pituitary, equine or chorionic gonadotropins. Testosterone, which produces growth in dwarf boys, is valueless in girls, and soon produces unpleasant masculinising effects. The use of thyroid extract is also futile. Stilboestrol or natural estrogens may be used orally in a cyclic way for three weeks, stopped fourth week, which will result in withdrawal bleeding. G

strol 1 mg each night for one week, 2 mg each night for the second week, 3 mg each night for the third week, stop for one week; then start a new cycle as before. If the bleeding occurs during administration, stop promptly and resume as above on the 3rd night of flow. Ordinarily this will produce twenty-eight day cycles.

This treatment is expected to produce mammary development, growth of sexual hair and the stimulation of external and internal genitalia (except the ovaries) to maturation. This development will have a favourable psychological effect on the patient who will regard herself normally acting and appearing female. After a year or two of this treatment the question of marriage may be considered. Marital life may be possible in a few cases but motherhood is out of question. Alteration in linear growth is not possible by any means, the bone age being the same as the chronological age.

CASE REPORTS

Case 1—OVARIAN INFANTILISM, RHEUMATOID ARTHRITIS, SPLENO-HEPATOMEGALY, AND ACHLORHYDRIA

HISTORY U H, a Hindu Kachhi girl, 20 years old, was brought for medical advice because of lack of menstruation, small size, insufficient development of secondary sexual characteristics, and painful swelling of joints (ankles, knees, wrists, elbows, and small joints of both hands,) making it difficult for her to get up, walk about or work, for the last six months. There was no physical asthenia or impairment of vision.

Born at full term, she was breast-fed by her mother. The childhood development was normal. There was no history of any disease in childhood except the usual children's ailments. The family history was negative.

PHYSICAL EXAMINATION Height 51 inches (127 cm); Sitting height 22 inches, Weight 66 lbs (30 Kg), Chest 25 inches, Abdomen 22 5 inches. General nutrition, good (See Fig 1, 2, and 3 on p 148).

Pilous system no hair in the axilla, scanty hair on mons veneris.

Bones no cubitus vulgus, no deformities.

Joints Knee, ankle, elbow, wrist and all the small-joints of the hand, on both the sides, were swollen, spindle-shaped, and tender to pressure with restricted movements. There was some wasting proximal to the affected joints. The appearance was typical of rheumatoid arthritis (Fig 4).

Mammary glands lack of glandular tissue, very scanty fatty tissue, infantile nipples and areolae.

Circulatory system Size of the heart definitely enlarged, the left border being 10 cm from the mid-sternal line, soft systolic bruit present at the apex conducted towards the axilla. B P 105/65 mm Hg.

Neck Short, no thyroid or thymus enlargement, no glands in the neck or axilla.

Lungs Normal.

Abdomen Spleen, enlarged 10 cm (4 inches) from the costal margin to the umbilicus, hard, not tender; Liver, enlarged 5 cm (2 inches) from the costal margin, not tender. Colon, some thickening and tenderness.

Eyes Fundus examination and visual fields were normal.

Genitalia Hypoplastic vulva, labia minora and clitoris small, hymen preserved, rectal examination showed a long vagina and complete absence of uterus, uterocervical ligament felt to be in the midline, ovaries not felt anywhere in the pelvis

X-Ray examination Skull normal, bones of the hands showed some osteoporosis, epiphyseal joining normal Heart was enlarged, lungs normal

LABORATORY FINDINGS Blood R B C 8 million per cmm, Hb 11.4 Gm per cent, some anisocytosis W B C 3250 per cmm; polymorphs 60 per cent, eosinophils 3 per cent and lymphocytes 30 per cent

Urine nil abnormal except the presence of two plus albumin



Fig. 4 (case 1)

Stools nil abnormal except the presence of cysts of *Entamoeba histolytica*

Blood calcium 11 mg per 100 ml of blood

Blood phosphorus Inorganic phosphorus 8.6 mg/100 ml (normal 3 mg), Alkaline phosphatase 22 units bodansky (normal 1.5 to 4 units bodansky)

Gastric juice Complete absence of free hydrochloric acid, even after histamin injection

Blood Kahn test negative

Hypophyseal follicle-stimulating-hormone (F S H) was reported to be excessive in the urine per 24 hours, other biological examination for 17-ketosteroids and for isogogens was not available.

Carbohydrate tolerance Exton-Rose test and carbohydrate tolerance curve were not carried out

This case, besides the main features characteristics of rudimentary or absent ovaries, shows signs of rheumatoid arthritis, hepatosplenomegaly, achlorhydria, and enlarged heart. The arthritis and enlarged spleen suggested Still's disease, but the age of the patient and the absence of enlarged lymph glands were against the diagnosis

Case 2 OVARIAN INFANTILISM, MACROCYTIC ANAEMIA, SPLENOMEGALY AND ACHLORHYDRIA

R, a Hindu girl of 17 sought advice because of frequency of stools with blood and mucus of three months' duration, absence of menstruation and failure of sexual development. There was nothing of significance in the past or family history.

PHYSICAL EXAMINATION: Height 130 cm (52 inches), sitting height 26 inches, weight 58 lbs. General appearance pale and puffiness; nutrition fair. (See Fig 5, and 6 on p 148)

Piloous-system smooth soft skin, not hairy, no hair in axilla or on mons veneris

Skeleton neck short, suggesting webbing. No other deformity. General articular laxity

Mammary glands Lack of glandular tissue, slight fatty tissue, infantile nipples and areolae

Genitalia Labia majora not properly developed. Vulva hypoplastic. Hymen preserved. Rectal examination showed complete absence of uterus and ovaries

Clinical examination of chest and abdomen showed nothing abnormal, except splenic enlargement, 5 cm from the costal margin

The X-Ray examination of the bones and chest was also negative

LABORATORY FINDINGS **Blood Count** R B C 1.4 mil per cmm. Hb 30 per cent, C I 1, W B C 3800 per cmm. Polymorphs 58 per cent, Lymphocytes 40 per cent, Large monocytes 2 per cent. **Erythrocyte Sedimentation Rate** 20 mm/hour (Westergren)

Blood Chemistry inorganic phosphorus 4.6 mg and alkaline phosphatase 11 units bodansky. **Stools** Typical findings of bacillary dysentery. **Kalm test** negative. **Gastric analysis** Complete achlorhydria. **F S H** was reported to be in excess in the 24 hour urine

This case also presents most of the typical features of rudimentary or absent ovaries, together with macrocytic anaemia, achlorhydria and bacillary dysentery

REFERENCES

- DELCASTILLO F B, DELABALZE F A AND ARGON J—Syndrome of Rudimentary Ovaries. *J Cl Endocrin* 7: 385-422 (June) (36 references)
- TURNER II H (1938) A Syndrome of Infantilism. Congenital Webbed Neck and Cubitus Valgus. *Endocrinology* 23: 566-574 (November)
- ALBRIGHT F, SMITH P AND FRASER R A (1942) A Syndrome characterized by Primitive Ovarian Insufficiency and decreased Stature. *Am J M Sc* 204: 625-648 (November)
- LISSER II, CURTIS I E, ESCAMILLA R F AND GOLDENBERG M B (1947) The syndrome of congenitally aplastic ovaries with sexual infantilism, high urinary gonadotropins, short stature, and other congenital abnormalities (25 cases). *J Cl Endocrin* 7: 665-687 (October), (9 references)

Critical Notes and Abstracts

NAIL CHANGES IN ARTERIAL DISEASE

The nails show specific pathologic changes in both arteriospastic and organic arterial diseases and are sensitive indicators of the severity of the underlying state. In arterio-spastic states, changes occur that may be grouped under the term of pterygium. They consist of a thinning of the nail fold and a widening of the cuticle. The normal abrupt demarcation between nail fold and cuticle, and between cuticle and nail plate is lost. In organic arterial disease the nails do not show these changes. There is rather a thickening, roughening, and darkening of the nail plate, which hides the nail head. An increase in arterial circulation by any means gives rise to a more nearly normal growth of the plate. Less specific changes include the growth of claw nails, or the loosening and shedding of the nail plate in severe disease of either vasospastic or organic origin. Painful nails are often an expression of the hyperesthesias of severe ischemia, in which operations for ingrown toe-nail usually cause gangrene. Primary infections of the nails are uncommon in peripheral vascular disease, but the nails may be involved in acral ulceration, or may show subungual abscess or an osteomyelitis of the terminal phalanx.—(EDWARD A. EDWARDS, M.D., *The New England Journal of Medicine*, September 2, 239-362-365, 1948)

A NEW TREATMENT FOR THE RELIEF OF OBLITERATIVE DISEASE OF PERIPHERAL ARTERIES by ISIDOR MUFSON, M.D., (New York, *Annals of Internal Medicine*, November, 29 903-913, 1948)

A procedure which can reproduce the immediate benefits of a sympathectomy and can be repeated if new developments make it necessary, should be a most useful means of treating obliterative peripheral arterial diseases. We have found that the intra-arterial infusion of a dilute solution of histamine may approach this ideal. In this article we are reporting its use in the femoral artery in patients with a severe insufficiency of the peripheral arterial circulation of the lower extremities caused by an endarteritis obliterans due to thromboangitis or to arteriosclerosis.

Method—An ordinary infusion burette was connected by means of a Y tube to a conventional sphygmomanometer, and a closed circuit established. With the skin and subcutaneous tissue anesthetized with procaine, a 2-inch, 20 gauge needle was introduced into the femoral artery. The appearance of pulsating, bright red blood in a syringe attached to the needle was evidence of entry into the artery. The pressure of the infusion was then raised or lowered until the pulsating blood could be seen only during each systole of the heart. The solution consisted of 500 c.c. of normal saline, to which was added between 1.38 and 2.75 mg. of histamine acid phosphate (Lilly) equivalent respectively to 0.5 mg. of histamine base. The infusion was given weekly, and if the symptoms were totally disabling, biweekly. The dropping rate was measured in the drip indicator during the diastolic fall in pressure during which inflow into the artery took place. It was found that between 2 and 5 drops per heart beat permitted an erythema of the thigh to develop without any subjective symptoms.

To date we have performed more than 500 arterial punctures. At no time have any local intra or extra arterial complications resulted.

The diffusion of radiosodium was studied in many patients

Results—The immediate objective responses to an intra-arterial infusion of histamine are striking. The degree and extent of these reactions are dependent upon the extent of the arterial block and the availability of a collateral circulation. The effects include a change in skin colour and temperature, a distension of the superficial veins and alteration in the rate of diffusion of radioactive sodium. As the solution of histamine begins to enter the femoral artery a definite erythema spreads over the thigh from the groin and buttock to the knee, becoming more intense as the treatment continues. The back of the leg, then the frong, and lastly the foot, become pink.

If the infusion is given too rapidly, thus permitting histamine to escape into the general circulation, erythema is observed to develop in the upper half of the body while the leg becomes only mottled and the foot even cyanotic. When the flow is slowed, however, permitting fixation of histamine in the leg, then the skin of the leg and foot becomes pink and the rest of the body remains pale. Such an observation is corroborative evidence of the futility of giving vasodilators intravenously. Its generalized dispersal opens the more sensitive and healthy arteries of the upper half of the body first. The dilatation diverts blood from the arteries of the lower half, this is valueless and may actually be dangerous.

A rise in skin temperature follows the erythema rapidly in the thigh, more slowly in the foot. The presence of erythema does not necessarily mean a rise in skin temperature, however. A rise in the temperature of the skin over the calf of the leg is most significant. It indicates that blood flow to the calf muscles has been increased to a magnitude where it might be expected to relieve the pains experienced while walking and sleeping.

No other treatment was used concurrently in the present study. Each patient had previously had one or more types of treatment.

Our results show that walking tolerance was raised to normal in about 85% of the patients treated, and the pain present during sleep was abolished in all.

Discussion—It has been shown that histamine given by arterial infusion is a powerful dilator of all the components of the peripheral vascular system. Its increase of the temperature of the skin and of radio-sodium diffusion indicates that all arteries are widened. The erythema of the skin which follows its use means that the precapillary sphincters are relaxed and the minute vessels are wide open. The superficial veins become visibly dilated. These physiologic responses are probably as short-lived as 6 hours, still improvement follows weekly infusion.

From the benefit in walking and sleep tolerance obtained, it is apparent that arterial blood flow after histamine infusion is effective and competent.

TEN SCIENCE ADVANCES OF 1948

The ten most important science advances made during 1948, as picked by Dr. Watson Davis, director of Science Services, are

1. Creation artificially in world's largest cyclotron of subatomic particles, called mesons, that may unravel mystery of composition of matter.

2 Achievement by jet plane of speeds well beyond the barrier of the speed of sound, opening a new air age

3 Demonstration that a single penicillin pill, swallowed a few hours after exposure, can prevent one of the two major venereal diseases, gonorrhea

4 Synthesis of glycerine from petroleum, making its commercial production independent of fat supply

5 Discovery of aureomycin and polymyxin, drugs effective against diseases unconquered by sulfa drugs and other antibiotics

6 Completion of the 200-inch world's largest telescope on Mt Palomar, Calif., seeing deepest ever into cosmic space

7 Authorization of two gigantic atom smashers, to produce three to five years hence sub-atomic "bullets" rivaling cosmic rays of three to seven billion electron-volts, vastly extending scope of nuclear physics

8 Commercial production of "low-temperature" rubber, giving chemical rubber superiority over natural rubber

9 Discovery of the fifth moon of the planet Uranus, with 30-hour orbit

10 Use of neutrons to explore the structure of matter by production of diffraction pattern photographs — *Science News Letter*, (December 18, 54 398, 1948)

MEDICAL ASPECTS OF THROMBOPHLEBITIS by EDGAR V ALLEN, Rochester, Minn. *Bulletin of the New York Academy of Medicine*, August, 24 491-501, 1948

In most instances the terms phlebothrombosis, thrombophlebitis, and venous thrombosis may be considered synonyms. While I am aware that some clinicians identify phlebothrombosis as a separate entity from thrombophlebitis, it has been my experience that differentiation is ordinarily of insignificant importance and in many instances impossible.

In general there are two causes of thrombophlebitis, injury to vein wall and changes in the blood. There are many instances of thrombophlebitis for which the mechanism is not readily apparent, for example, thrombophlebitis following an abdominal operation but we do not know that this slowing of flow causes thrombophlebitis. The cause of superficial thrombophlebitis of patients who have cancer of the lung, stomach or pancreas is also unknown.

In a case of superficial thrombophlebitis, the physician should determine first whether the vein has been injured by trauma or injection. He should consider phlebitis occurs commonly in varicose veins probably as a result of destruction of intima, slowing of blood flow and reduced oxygen saturation of blood. He should consider thrombo-angitis obliterans because superficial thrombophlebitis occurs at some time in the course of 40% of patients with thrombo-angitis obliterans. He should think of polycythemia vera which notoriously provokes both arterial and venous occlusion. He should think of malignancy, inasmuch as carcinoma of the bronchus, stomach and pancreas is not infrequently the direct cause of venous thrombosis. Finally, superficial thrombophlebitis may occur without apparent cause, the situation is comparable to tonsillitis, appendicitis and cholecystitis except that a bacterial cause is not commonly apparent in phlebitis.

The treatment of superficial thrombophlebitis is of course the treatment of the cause of it, when that be determined. Sur. 71 Phleb.

itself may require no specific treatment. Indeed, the commonest type of superficial venous thrombosis, that following injection treatment of varices is ordinarily given no specific treatment. It is surprising how inconsistent we are in our attitude toward phlebitis in varices, caused by injection of a sclerosing solution and that occurring spontaneously. When the phlebitis is intentionally provoked the patient is kept active. When phlebitis occurs spontaneously in varices it has been customary to restrict the patient to bed. There is no satisfactory explanation of this inconsistency.

If thrombosis progresses close to the juncture of the greater or lesser saphenous systems with the femoral or popliteal veins respectively, its progress must be halted either by anticoagulants or by surgical ligation and division. Failure to do so may permit extension into the femoral or popliteal vein from which a pulmonary embolus may arise. Also important to remember is the possibility of thrombophlebitis of the deep veins associated with superficial phlebitis. If any evidence of this exists it is well to use anticoagulants.

In a case of deep thrombophlebitis the physician should think first of the cause of which the three most common are operation, delivery and bed rest as a result of illness of a medical nature. It may result from trauma, from many infectious diseases as, for example, pneumonia and tularemia, from polycythemia or leukemia or from pregnancy. If none of these or malignancy or thromboangitis obliterans are apparent on careful examination, the physician will need to consider that the thrombophlebitis of the deep veins is of the "idiopathic" type. One treatment of deep thrombophlebitis, is, of course, the treatment of its cause if that can be determined. However, there is need for immediate treatment, first to prevent pulmonary embolism, second, to restrict the thrombosis to as small an extent as possible in order to lessen the chronic venous insufficiency which is an inevitable consequence of such a thrombosis, edema, varices, stasis dermatitis and ulceration.

Our discussing the active treatment of thrombophlebitis, I will dismiss about 21 of veins with a few sentences. I believe that anti-coagulants will do as much as ligation or more. I prefer anticoagulants to ligation in all cases except when anticoagulants are contraindicated, and when they have not been effective. As to anesthetization of appropriate sympathetic ganglia, this procedure is said to lessen pain, fever, and edema in acute venous thrombosis. In my experience, with rare exceptions, the pain requires only aspirin or codeine, the fever is usually mild and I have observed little or no effect on edema. The statement that this procedure lessens chronic venous insufficiency, seems on very insecure footing. Finally, I believe that elevation of the extremity and the application of warm moist packs has the same physiologic effect on circulation of a limb as sympathetic block and is to be preferred because of its simplicity. The contribution to the treatment of thrombophlebitis which is the greatest interest now is treatment with the anticoagulants, heparin and dicumarol.

Heparin should always be used when an anticoagulant effect is needed quickly and when reliable laboratory determination of the value of prothrombin in the blood is not available. Intravenous injection of 50 mg of heparin (5 cc solution) every four hours is generally the most satisfactory mode of administration. Dicumarol should be used when-

ever an anticoagulant effect is needed over a period of days, weeks, months, or years, provided the determinations of the value for prothrombin in the blood are reliable. When both a rapid and a prolonged effect of an anticoagulant are desired, heparin and dicumarol should be administered simultaneously, administration of heparin should be discontinued when dicumarol has produced a satisfactory effect on prothrombin.

The Dosage of Dicumarol —Three hundred milligrams of dicumarol are given on the first day and 200 mg on the second day. In each subsequent day when the prothrombin is more than 20%, 200 mg are given. On any day when the value for prothrombin is less than 20%, dicumarol is withheld. There are minor variations of this program depending on sensitivity or resistance of a patient's prothrombin to dicumarol.

The Prevention and Control of Hemorrhage —The best method of preventing hemorrhage is to use dicumarol expertly. Even then, hemorrhage may occur. When epistaxis, hematuria and local ecchymosis are minor we do not ordinarily alter dosage but observe the patient for signs of more extensive bleeding. If bleeding from an operative wound is continued or marked, synthetic vitamin K (menadione bisulfite) should be administered intravenously in amounts of 60 mg and transfusion of fresh blood should be used to restore the blood that has been lost. The injection of vitamin K can be repeated at two hours intervals once or twice as needed.

How long should the physician continue anti-coagulant therapy and what should he do once the acute phase is over? Ordinarily, in deep thrombophlebitis we continue anticoagulant therapy for about 10 days unless there is evidence of progressive venous thrombosis. I am uncertain about ambulation in the presence of acute thrombophlebitis of deep veins. I believe a median course is advisable as far as activity is concerned. Usually I recommend ambulation when edema has largely or wholly disappeared.

The final consideration in deep thrombophlebitis is the management when the patient becomes active. This can be stated in two words: Prevent edema! This is accomplished by adequate bandaging. The test of adequacy is whether or not edema occurs when the bandage is worn. Ordinarily, the cloth-elastic bandage known as the Ace bandage or tensor bandage is inadequate. The best bandage, by all means, is the pure gum rubber bandage 3 inches wide and 15 feet long. No attempt is made to bandage above the knee. The edema there disappears in time. The bandage is applied in the morning usually over a hse stocking. If there is much perspiration it is well to change the stocking and re-apply the bandage at noon. Naturally it is not worn at night. I know little advantage to instructing the patient to sit with the leg on a stool or chair or to elevating it while he is in bed. Once every month the patient discards the bandage for one day. If edema occurs the bandage is worn for another month. Many patients can discard the bandage forever within three to six months.

TREATMENT OF HYPERHIDROSIS AND SYMMETRIC LIVIDITIES OF THE FEET by J. G. HOPKINS, M.D., A. B. HILLEGAS, M.D., R. B. LEDIN, M.D., G. C. REBELL, M.D. and E. CAMP, M.D. New York. (*Archives of Dermatology and Syphilology*, May, 1948, 57: 850-57)

In the course of a study of dermatophytosis in infantry troops numerous cases of severe inflammation of the feet were encountered which could not, on the basis of our evidence, be ascribed to fungous or to pyogenic infection or to sensitization to footgear. It appeared that the essential cause was hyperhidrosis. The cases were of two types.

Diffuse Hyperhidrosis—The larger group was of men who showed excessive sweating of the entire foot. The skin was often macerated. There was frequent erythema and edema of the dorsal and plantar surfaces of the toes and often denudation of the corneal epithelium and fissures on the webs of the toes. In a number of men definite non-suppurative cellulitis of the toes developed. All toes were uniformly involved, and the complaints of the men were of burning and pain rather than of itching.

In 201 such cases fungi were demonstrated in only 37 per cent, although some were searched on eight successive occasions and the median number of examinations was two. This frequency was somewhat lower than in samples in the general military population.¹⁴

Symmetric Lividities—A curious type of lesion was seen in many men with, and in a few without, general hyperhidrosis. They presented on pressure areas sharply bordered plaques of white soggy skin surrounded by narrow violet-red borders. The plaques often appeared slightly raised. Little beads of clear fluid appeared on their surface, even when the more normal surrounding skin was fairly dry. The areas were often exquisitely sensitive to touch. They occurred most frequently on the sole of the heel and at the heads of the metatarsals, but also on the plantar and lateral surfaces of terminal phalanges and, in fact, anywhere that the shoe or a neighbouring toe exerted pressure.¹⁵ Various hypotheses have been advanced as to the causation of these lividities, but all observers have noted their association with hyperhidrosis. Pressure and friction on skin macerated by sweat may be an adequate explanation. Denudation of the horny layer of an edematous area may have permitted exudation of interstitial fluid, which gave the appearance of local sweating.

Treatment—In the treatment in these cases, formaldehyde and alum were used in an effort to reduce sweating and tannic acid with the purpose of preventing maceration. Of numerous preparations the following ones seemed most useful.

1 Foot baths containing 4 per cent potassium alum were used in 45 cases of severe diffuse hyperhidrosis with improvement in about 50%. It seemed that most useful treatment in cases with much inflammation.

2 A 4 per cent solution of formaldehyde painted on the affected areas was used in 76 cases of symmetric lividity. It seemed to give the most prompt relief in this condition. Improvement was recorded in 88% and complete clearing 83%. It was also used in 172 cases of diffuse hyperhidrosis and was frequently of temporary benefit.

3 For dressing denuded areas, which frequently develop on¹⁶ hyperhidrotic feet, tannic acid ointments seemed especially 'useful'. The most satisfactory preparations were 10 to 20% tannic acid in a "carbawax" (a polyethylene glycol) base.

4 For prolonged treatment in these cases, powders were more practical and probably of greater benefit. Of various alum powders, one composed of 25% exsiccated potassium alum and 75% talc appeared the most satisfactory. Powders containing 5% paraformaldehyde in

talc or bentonite gave more permanent and decisive results in most cases and seem to deserve more trial in the treatment of hyperhidrosis. Powders of from 10 to 20% tannic acid appeared less effective.

We were naturally apprehensive about irritation or sensitization from formaldehyde, on account of the known occurrence of occupational dermatitis from its use. However, of 48 patients who used the paraformaldehyde powder only, none showed evidence of dermatitis. In 2 patients fissures developed while they were receiving treatment, which were probably due to excessive drying by the powder. Of 218 patients whose lesions are painted with the 4% solution of formaldehyde, with or without the powder, dermatitis developed in 5 (2.3%), but in no case was it severe or persistent. In 20 of these patients fissures developed while they were receiving treatment. The patients were to some extent selected, as none of the formaldehyde preparations are used for patients already showing signs of eczematization. If used with judgment, we believe that both preparations, especially the paraformaldehyde powder, will prove helpful in the treatment of hyperhidrosis.

INSULIN MIXTURES AND CONSERVATION OF INSULIN

by RUSSELL M. WILDER, M.D. Rochester, Minn. (*American Journal of Medicine*, 1948, 5: 582-586)

My colleagues and I have had almost 10 years of experience with insulin mixtures. We are now obtaining reasonable control of glycosuria with only one injection daily in a fair majority of cases of what we call grade 4 diabetes, that is, cases in which the diabetes is of such severity that the total daily insulin requirement of the patient exceeds 30 units.

We advocate preparation of the mixture in the syringe according to the technic herein described. The procedure has the disadvantage of being somewhat difficult to teach to patients, and for that reason it is unsuitable for the very ignorant or for those who are handicapped by poor vision. For such individuals we resort to other methods of insulin administration.

In most cases, however, the patient has been able to acquire the technic of making mixtures, and the advantages of the procedure are important. They are (1) that in a large proportion of all cases, adequate control of glycosuria is obtainable with a single injection daily, (2) that continued insulin action is assured over the night with little danger of reaction at that time, and (3) that the total daily unitage of insulin required is usually somewhat smaller than that necessary for comparable control of glycosuria when dependence must be placed either on soluble insulin or on protamine zinc insulin used alone.

Another great advantage of insulin mixtures prepared in the syringe is that each component of the mixture can be adjusted to fit the needs of the individual. Also in our experience the requirements of the individual are likely to change from time to time.

In the majority of cases, 2 parts of soluble insulin added to one part of protamine zinc insulin best fits the needs most of the time. In other cases other ratios have been advantageous. The appropriate ratio rarely exceeds 3 parts of soluble insulin to one of protamine zinc insulin. A ratio lower than 1:1 usually implies that a ratio of 1:1 will do all that is required.

In cases of mild diabetes, with a total daily requirement of less than 20 units, the condition can be handled safely by the use of only protamine zinc insulin. In cases of severe diabetes a dose sufficient to prevent gross glycosuria after meals commonly precipitates an insulin reaction in the night. The night is a bad time for a reaction because the patient and his family are asleep. Furthermore, the hypoglycemia which develops from an overdose of protamine zinc insulin comes on so gradually as to be almost symptomless, and the patient may remain quite unaware that his blood sugar has fallen to unphysiologic levels. This may go on unrecognized for quite a long time.

As a rule, vague but unpleasant symptoms develop fairly early even when the patient experiences none of the symptoms which commonly are attributed to insulin reaction, symptoms such as sweating, anxiety, tremor and diplopia, with later loss of consciousness and convulsions. A fair proportion of diabetic patients who come to the Mayo Clinic using protamine zinc insulin complain on arrival of headaches, backaches and leg aches, associated with feelings of exhaustion and weakness with incapacity for mental concentration. Their symptoms disappear soon after the dose of insulin has been lowered. In a few instances, actual mental deterioration has been evident, and then recovery has been delayed.

The symptoms mentioned also are observed in patients who use mixtures of soluble and protamine zinc insulin, especially when the amount of protamine zinc insulin is large. Therefore, when the total insulin requirement is large, involving the use of more than 20 units of protamine zinc insulin combined with 40 units of soluble insulin, we now advise either increasing only the amount of soluble insulin in the mixture or abandoning the attempt to obtain control of glycosuria with a single injection daily and giving a supplementary dose of soluble insulin before the evening meal.

Control of glycosuria in some instances is less satisfactory with mixed insulins than we should like to have it. In certain cases, results superior to those obtainable with mixed insulins are to be had with injections of soluble insulin given 3 to 4 times daily or with protamine zinc insulin and soluble insulin administered in separate sites. In a few cases of severe diabetes, best control has resulted from giving soluble insulin before breakfast, and globin insulin before the midday meal. The action of globin insulin seems not to extend much beyond the 16th hour. With 2 injections a day, however, one of soluble and one of globin insulin, this difficulty is overcome.

Use of extemporaneous mixtures of protamine zinc insulin and soluble insulin in one syringe calls for precaution to prevent introduction of one kind of insulin into other vial. An appropriate volume of air is first injected into the vial of protamine zinc insulin, and the needle is withdrawn without any insulin being permitted to enter the syringe. Then the desired dose of soluble insulin is drawn into the syringe in the usual manner. After this, the needle is again inserted into the vial of protamine zinc insulin, and the desired dose is allowed to flow into the syringe, and to overlap the soluble insulin which is there already. The 2 insulins are then mixed by drawing a small bubble of air into the syringe, inverting the syringe several times and then expelling the bubble.

Usually with diabetes of moderate severity, adequate information is obtainable by testing urine twice daily, before breakfast and before

supper. Sugar in the urine before the morning meal calls for more protamine zinc insulin whereas sugar before the evening meal demands more soluble insulin.

In most cases, when reasonable control of glycosuria has been effected, it is inadvisable to make changes in the doses of the 2 kinds of insulin more frequently than has been suggested. Factors other than insulin notably emotional disturbances and variations of food intake may be responsible for transient glycosuria. On the other hand, the occurrence of a bona fide insulin reaction usually calls for lowering the next day's dose of insulin.

Considerable advantage attends the continued use of some protamine zinc insulin in emergencies. Although multiple injections of soluble insulin are also made, prolonged action of the protamine zinc insulin is helpful to insure a continuous insulin effect day and night. When the patient has been maintained either with one injection daily of protamine zinc insulin alone or with a mixture of soluble insulin and protamine zinc insulin, the dose of protamine zinc insulin or that of the mixture is continued as before, with additional injections of soluble insulin made at intervals. Freshly secreted urine is tested for sugar—and for diacetic acid when necessary—every 3 hours, and appropriate doses of insulin are given after each test.

Great saving in the use of insulin in cases of diabetic patients who are grossly overweight can be accomplished by not using insulin at all, except in periods of emergency. The treatment of choice for the obese diabetic patient is a reducing diet, not insulin. When such patient is given a diet as low in calories as or lower than his basal calorie needs, he usually becomes aglycosuric without insulin. The giving of insulin may only stimulate his appetite and add to his desire to eat beyond his diet. Also when the body weight of such a patient has been lowered to the standard weight for height a maintenance diet usually can be tolerated without insulin.

VITAMIN B-12 THERAPY IN PERNICIOUS ANEMIA. I. EFFECT ON HEMATOPOIETIC SYSTEM *by* B. E. HALL, M.D. and D. C. CAMPBELL, M.D. Rochester, Minn. Proceedings of the Staff Meetings of the Mayo Clinic, December 8, 23. 584-590.

We have studied the effects of B-12 therapy in 11 patients who had pernicious anemia in severe or moderately severe relapse. Eight of the 11 patients had not had previous anti-anemic therapy, inasmuch as the diagnosis was not established until after admission to the Clinic. Two of the remaining 3 patients had had short courses of parenteral liver therapy 4 and 3 years previously, and the last patient had received liver extract by mouth over a 3 year period but had taken it in inadequate dosage and for only short intervals for one year prior to admission. All 11 patients have been under observation for from 1 to 5 months.

Prior to the beginning of treatment, the erythrocyte counts of 8 of the 11 patients were less than 2,000,000 cells per cubic mm. of blood, and in 3 patients they were between 2,500,000 and 3,000,000. After the administration of vitamin B-12, reticulocyte peaks of from 7.2 to 39.0% were noted in the group of cases in which the initial erythrocyte counts were less than 2,000,000 and from 2.1 to 9.7 in the other group. The reticulocyte peaks in all cases occurred from the fourth to the seventh day after institution of therapy. In 6 of the 11 patients, the erythro-

cyte counts levelled off instead of continuing to rise after the counts had exceeded 8,000,000. Plateaus of this type lasted from 1 to 3 weeks.

Concomitant with the increase in number of erythrocytes, values for leukocytes and blood platelets returned to normal in all patients in which they were sub-normal prior to the institution of therapy.

Approximately 1.0 microgram of vitamin B-12 is the equivalent of one U.S.P. unit of extracts of liver or stomach mucosa. The optimum treatment and maintenance dosages for our patients have not yet been established.

Sternal aspirations were performed in 10 of the 11 patients prior to administration of vitamin B-12. Erythrocytic regeneration in 7 was of the megaloblastic type, and in one it was of the normoblastic type. Serial sternal aspirations performed after the administration of vitamin B-12 showed rapid conversion from megaloblastic to normoblastic regeneration, which was virtually complete in 48 hours in patients who were given relatively large doses of the vitamin.

2 EFFECT ON THE GENERAL CLINICAL AND NEUROLOGIC MANIFESTATIONS

We studied 11 patients with pernicious anemia who were given a course of vitamin B-12 therapy. All 11 were in severe or moderately severe relapse prior to the institution of treatment, and all had the usual symptoms attributable to the attendant anemia. Six had glossitis, 3 had peripheral neuritis, and 6 had peripheral neuritis and early or moderately advanced subacute combined degeneration of the spinal cord.

Following the intramuscular administration of vitamin B-12 and concomitant with improvement in the anemia, a gradual return of strength and mental alertness, and improvement in appetite with consequent gain in weight were noted. Soreness of the tongue and mouth disappeared within a few days and regeneration of lingual papillae usually was complete in from 4 to 6 weeks.

Varying degrees of improvement in the neurologic manifestations were observed in 3 patients who had peripheral neuritis, and in 5 of 6 patients who had peripheral neuritis and subacute combined degeneration of the spinal cord. In 3 of 6 patients with combined degeneration of the cord, the rate of improvement appeared to be remarkably rapid for the degree of neurologic involvement noted before treatment was begun.

WHAT THE GENERAL PRACTITIONER SHOULD KNOW ABOUT OPHTHALMOSCOPIC EXAMINATIONS *by* FREDERICK A. DAVIS, Madison, *Postgraduate Medicine*, December, 4, 473-500

The general practitioner should use the ophthalmoscope in his daily work, since it can provide a great deal of valuable information in the study of patients. Many ocular diseases are but local manifestations in the eye of common general ailments.

Before entering upon a description of the technique of ophthalmoscopy let us first consider some of the basic rules which should govern everyone who uses the ophthalmoscope. First, to obtain a satisfactory view of the fundus, the media must be clear. By that I refer to the cornea, aqueous crystalline lens, and the vitreous. If there should be clouding of these structures from various causes, difficulty will be encountered in visualizing the fundus and consultation may be necessary.

Second the size of the pupil is of great importance, especially when one is not skilled in the use of the ophthalmoscope. Should a clear view of the disk and retina prove impossible through the undilated pupil, a weak mydriatic such as ephedrine, 3%, or ephedrine, 5%, may be used to relax the sphincter. A complete and thorough study of all parts of the fundus is usually impossible unless the pupil is dilated. These drugs produce a moderate dilatation of the normal pupil in 15 to 30 minutes, although at times two instillations may be required if the iris is rigid. Their action is not excessive or prolonged and it can be quickly neutralized by the use of a drop of a miotic, such as pilocarpine, 2%, or eserine, 0.5%.

One should bear in mind that careless or indiscriminate dilation of the pupil in subjects of 40 years or over may, in rare instances, precipitate an acute rise in intraocular pressure, such as is seen in acute glaucoma, in an individual already the subject of the disease in its early or latent stage, which has been unrecognized. There, it is always wise to use a counteracting miotic at the conclusion of the examination whenever the pupil has been dilated for diagnostic purposes.

Technic of Examination—The direct method utilizing the electric self-luminous ophthalmoscope, is the simplest and most easily mastered technic yet devised. I think it helpful for both patient and examiner to be comfortably seated in a dark or semi-dark room. The examiner should sit on an easily movable stool on the patient's right side when examining the right eye, and on his left side when examining the left eye. The examination is easier if the examiner's and the patient's heads are on approximately the same level. The patient should be told to look straight ahead or slightly to the nasal side, directing the gaze of the eye not under examination at some object, such as a white disk of paper pasted upon the opposite wall of the room.

The ophthalmoscope should be held vertically in the examiner's right hand before his right eye when examining the patient's right eye, and in the left hand before the left eye when examining the patient's left eye. With the instrument held close to his own eye the examiner should approach the patient's eye, at the same time steadying the patient's head by placing his hand on the back of the head or neck. The light from the ophthalmoscope is directed into the patient's pupil a few inches from the eye until a fundus-glow is seen. The examiner then continues to approach the eye as closely as possible without touching it, whereby details of the eye ground will come into view. If the examiner has a moderately high refractive error, he should wear his glasses, but they mechanically interfere somewhat with the examination and may be discarded if desired.

I suggest that the general practitioner familiarize himself with the appearance of the fundus in the following five basic conditions:

1. He should know the normal fundus and its common variations.
2. He should be able to recognize abnormal blurring, congestion, swelling, or choking of the papilla, which is commonly seen in optic neuritis (papillitis) and in choked disc (papilledema).
3. He should be able to recognize pallor of the optic disk and varying degrees of atrophy.
4. He should be familiar with true glaucomatous cupping of the nerve head and be able to differentiate it from physiologic cupping.

5 He should be able to recognize abnormalities in retinal vessels, particularly constriction or narrowing, spasm or obliteration, irregularities in caliber, tortuosity, beading, changes in colour, arteriovenous compression, and hæmorrhages and exudates in the retina

Retinal hemorrhages and exudates frequently occur in the course of various general diseases, such as diabetes, hypertensive cardiovascular and renal diseases, the toxæmia of pregnancy, etc. Their site, source and character are varied, and the general practitioner may at first find it difficult to explore all their implications. It is important, however, for him to be able to recognize their presence, thereafter he may seek assistance concerning their nature and significance from someone more thoroughly trained in ophthalmoscopic interpretation.

Ophthalmoscopic Appearance of the Normal Fundus—The appearance of the normal fundus may vary considerably in different individuals, depending upon age, complexion, race, etc. It is, therefore, important that the practitioner become familiar with these variations in order that he may not confuse them with pathologic changes.

Systematic writers frequently describe the normal fundus under three different types, to which I should like to add a fourth, (1) the uniform stippled fundus (2) the tasseled fundus, (3) the albinotic fundus, and (4) the mixed-type fundus.

These variations depend, in a large degree, upon the amount, type, and distribution of the pigment in the choroid and the pigment epithelium of the retina. The intensity of the pigmentation usually follows the color of the hair and skin of the individual, varying with the blond and brunette types.

The macula is located in the line of the visual axis at the posterior pole of the eye. Its center, the fovea, lies about 3.5 mm or $2\frac{1}{2}$ disk diameters to the temporal side of the disk and slightly below the horizontal meridian. The usual ophthalmoscopic appearance of the macula consists of a small white spot surrounded by an area more deeply pigmented than the rest of the retina. This white spot is nothing but a reflex from the curved surface of the macula at the fovea. Its form and shape change, therefore, as the light from the ophthalmoscope is moved in different positions. The sharp contour and brightness of the reflex usually diminishes with advancing years. The macular area can be best observed if the patient is directed to look at the right in the ophthalmoscope, providing the pupil is well dilated. If the pupil is not dilated, this procedure is not satisfactory, since the pupil will contract sharply, and the light reflex from the cornea may prove annoying or may make it impossible to view the macula under these conditions. The inexperienced may have to search for the macula and may find it helpful to note that the fine terminal retinal blood vessels which surround this are a point toward it but end before reaching it.

The optic disk or papilla is the point of greatest interest in the fundus. It may be located by following the larger vessels to the point where they converge or emerge on the surface of the retina. It can best be observed if the patient is directed to look slightly in, or nasalward, since it lies to the nasal side of the visual axis and is, therefore, out of line when the examiner looks into an eye whose gaze is directly forward. When examining the disk it is well to keep in mind the following points: (1) form and size, (2) color, (3) margins (4) surface level (excavation or protrusion), and (5) blood vessels.

If the physiologic cup is quite large it may be confused with the pathologic cupping seen in glaucoma. The criterion for differentiation of the physiologic cup from that of glaucoma is that the former does not extend to the border of the disk. Usually some normal, healthy nerve fibres intervene between it and the margin of the disk, which is recognized ophthalmoscopically by the light pink coloration of the tissue. The cup of glaucoma extends to the border of the disk at some point. At times, however, the physiologic cup has a shelving edge as it approaches the temporal margin of the disk and so resembles the cupping of glaucoma that other tests such as plotting of the fields and blind spots and measuring of the intraocular pressure, must be used in order to establish its true nature.

CAUSES OF PRE-ECLAMPSIA

Dr Ernest W. Page in his recent study of symptoms in eclampsia states that the philosophy of treatment in eclampsia cannot rest upon the principle of combatting symptoms with therapeutic weapons, but should rest upon assisting the maternal organism to keep its own compensatory efforts within bounds of safety, preventing damage to vital organs and removing the cause of the disease by termination of the pregnancy whenever that may be done with safety to both mother and child.

According to Dr. Page such assistance may be based upon current understanding of the disturbances which underlie each symptom. The placenta is considered to be in some way related to the cause of pre-eclampsia and disturbances in the functions of placental transmission are suggested by the interruption of the normal growth rate of the fetus after the onset of toxemia. Disturbances of secretory function are reflected by the decreased urinary excretion of estrogen and progesterone end-products during pre-eclampsia. The occurrence of epigastric pain usually indicates that acute hepatic disease exists and that such a case should be classified as severe, regardless of blood pressure or urinary findings.

The use of Heparin, a direct antagonist of thromboplastin, although not recommended for general use, has been of demonstrated therapeutic value when used experimentally for relieving epigastric distress. More toxemic mothers die from the secondary effects of the hypertension of eclampsia than any other cause. This may be due to nervous or chemical factors. These effects may be observed directly in the ocular fundi, where arteriolar constriction, edema, exudates, and hemorrhages occur. Therapeutic measures suggested by Dr. Page, are the use of pharmacologic agents, sedatives, prophylactic digitalization, and in the more fulminating cases termination of pregnancy.

Another characteristic sign of pre-eclampsia is the occurrence of gross amounts of protein in the urine. There are other alterations of tubular function in pre-eclampsia, instead of rejecting the amino acid histidine, as the tubules do in normal pregnancy, there is a return to the non-pregnant status and the histidine is completely reabsorbed.

In normal pregnancy, it is believed that an increased level of steroid hormones originating from the placenta and adrenal cortex influences the distal tubules to reabsorb larger proportions of sodium and water. The diminution of plasma osmotic pressure resulting from dilution

be another factor. It is suggested that amino methionine be added to the diet of pre-eclamptic patients, this agent is known to be of value in protecting the liver against a variety of insults. When pre eclampsia supervenes, it would seem that the additional edema may perhaps best be attributed to the diminished glomerular filtration and oliguria may in themselves lead to a fatal outcome, it seems quite proper that the intake of the sodium ion should be restricted and also displaced by the judicious use of such drugs as ammonium chloride.

Electroencephalographic studies of women who have had toxemias suggest that those who develop convulsions during the course of pre-eclampsia have an underlying cerebral dysrhythmia. It is for this reason that the prophylactic use of either dilantin or mesantoin on all pre-eclamptic patients seems warranted, in the opinion of Dr. Page, since these agents have proven their worth in the prevention of epileptic convulsions and seem sufficiently devoid of harm.

(Page, Ernest W. M.D., *The Physiologic Basis of Symptoms in Eclampsia*, California Medicine p. 1, January, 1949)

Page, E. W., *The Mechanism of the Histidinuria of Pregnancy*. American Journal of Obstetrics and Gynecology 51: 533, 1946

Rosenbaum M., and Miltby G. L. Cerebral Dysrhythmia in Relation to Eclampsia, Archives Neurology and Psychology 49: 204, 1943

EFFECT OF CALCIUM GLUCONATE IN TREATING THE BITE OF A FEMALE LATRODECTUS MACTANS

The distribution of the spider *Latrodectus mactans*, present in all but seven states in the United States, is widening and spreading to the cities according to a recent report by Greer. Greer stresses the need for knowledge of this clinical entity, since many victims of spider bites are subjected to needless operations. Symptoms often simulate acute surgical conditions of the abdomen and arachnidism should be considered in the differential diagnosis of this condition. An appalling record of human suffering had been checked back to *Latrodectus mactans* and its prototypes.

Cases of arachnidism reported represent only a small fraction of the actual number that have occurred since many are not reported. Its curtailment in rural areas can only be accomplished by unified efforts. Parasitic insects of the black-widow spider can be encouraged. Evidence of arachnidism rests largely on the statement of patients who have been bitten by insects answering the description of *Latrodectus mactans*. In some cases the victim or observers have caught the spider and brought it to be identified.

The species *Latrodectus mactans* have been found in dark corners and in clothes closets. They are cannibalistic, feeding on each other whenever the opportunity presents itself. The nickname "black widow" given to the female of the species arises from its habit of capturing and feeding on the much smaller male after copulation.

The globose abdomen of the female stands out like a highly polished black pearl. It is attached by a slender pedicle to the smaller cephalothorax. The body averages 1.27 cm in length. Slender pointed legs when expanded have a span of 3.8 to 5.1 cm. Legs and body are a glossy black and are covered by short black hairs. On the ventral surface of the abdomen there is a red marking resembling an hourglass. Dorsal to the spinnerets in the midline of the convex surface of the abdomen are additional red markings.

The full grown female, particularly, when distended with eggs, appears from experiments to be the most poisonous. When cornered or compressed, as between skin and clothing the spider bites in self-defense. The male is usually ignored because of its small size, timidity, and scarcity. About an hour after a bite the victim writhes in agony, terror-stricken and expresses fear of death. The venom has been stated to be a toxalbumin. Its most damaging effect is on nerve endings. It is a thick, translucent, oily, lemon yellow-coloured fluid, acid in reaction, from which a hemolysin and arachnolysin have been isolated.

The clinical picture has been divided by Blair into three stages: lymphatic absorption of the injected venom characterized by pains in the bitten area, and absence of systemic effects; the stage of vascular dissemination, characterized by explosive onset of widespread agonizing muscular pains and a condition of profound shock, and elimination of the venom characterized by hypertension, diaphoresis, gradually diminishing muscular pain and evidence of renal damage—this stage is suggestive of acute toxic nephritis. The syndrome in six patients presented a similar pattern. Greer adds that burning of the soles of the feet in arachnidism may be pathognomonic.

The patients in his series were given 10 c.c. of 10 per cent calcium gluconate intravenously followed by a saline infusion containing 10 c.c. of 10 per cent calcium gluconate. An ice bag was applied to the affected area. Two patients in profound shock responded well to this treatment. Patients were out of bed the next day and back to work on the fourth day. Greer states that immediate and prolonged relief of muscle spasm and pain was obtained in all cases with calcium gluconate therapy.

(Greer William E. R. M.D. Arachnidism. The New England Journal of Medicine Vol. 240 p. 5, January 6, 1949.)

Thorpe R. W. and Woodson W. D. Black Widow. America's Most Poisonous Spider. 233 pp.

Chapel Hill: University of North Carolina Press, 1945.

Blair A. W. Spider Poisoning. Experimental Study of Effects of Bite of Female *Lactrodectus* in Man. Archives of Internal Medicine 54: 831-843, 1943.)

REFLEXES IN MORPHINE AND METHADON ADDICTION IN CHRONIC SPINAL DOGS

Methods for preparing long-surviving, chronic spinal dogs, and methods for recording spontaneous activity and hindlimb reflexes in such preparations are described in a recent paper by Wikler and Frank. They believed that addiction studies in chronic spinal animals might be expected to contribute to present day knowledge of the neurophysiologic aspects of tolerance to and physical dependence upon opiate drugs. Twelve dogs were prepared by aseptic transection of the spinal cord between D-10 and D-12 segments under nembutal anesthesia. In the first few animals, a simple transection was made and after hemostasis was secured the muscles, fascia and skin were closed with silk sutures. In others, a segment of spinal cord 3.5 mm. in length was removed and the dura was closed with a silver clip at the site of corectomy before closing the operative wound.

No appreciable differences between the two types of preparations were noted post-operatively, but removal of a segment of cord afforded objective evidence of complete transection before autopsy. In recording the reflexes, no attempt was made to limit the response to one joint but the main component of each response was selected for measurement. Both "isometric" and "isotonic" methods were employed. In both

cases, sufficient reproducibility of the position of the preparations in repeated experiments was obtained by using the iliac crest and sacral spine as reference points. "Isometric" recording devices included a strong spring lever and a pneumatic syphon arrangement, the test limb being fixed rigidly to the device by a double cuff applied to the leg and foot on either side of the ankle. In each experiment about 50 knee jerks, 10 extensor thrusts, three to six ipsilateral flexor, and three to six crossed extensor reflexes were recorded.

The effects of single doses of drugs were studied by recording spontaneous activity and reflexes of the hindlimb before and at various intervals after administration of the drug. In the case of morphine and methadon, injections were given subcutaneously, since preliminary experiments showed that the peak effects were reached at this time. The addiction periods varied in length from 29 to 103 days each. It was found that in chronic spinal dogs, single doses of morphine or methadon depress the ipsilateral flexor and crossed extensor reflexes, enhance the ipsilateral extensor thrust in most instances, and have but variable effects on the knee jerk. After large doses of morphine (100-150 mgm/kgm) or methadon (40-50 mgm/kgm) tonic and clonic convulsions appear in the segments rostral to the transection but not below it.

The investigators, Wikler and Frank, also found that during addiction to morphine or methadon tolerance develops to the depressant effects of morphine and methadon on the ipsilateral flexor and crossed extensor reflexes, but not to the excitant effects on the ipsilateral extensor thrust. As addiction is continued, the pre-injection values of the ipsilateral flexor and crossed extensor reflexes increase, both with respect to amplitude and duration of the response. The ipsilateral flexor and crossed extensor reflexes continue to increase in magnitude, while the knee jerk and ipsilateral extensor thrusts diminish after abrupt cessation of morphine or methadon.

Hyperactivity of the ipsilateral flexor reflex may persist for as long as four months after withdrawal of morphine. At about the same time as the spontaneous activity in the hindlimbs, after the withdrawal of morphine or methadon, signs of abstinence such as restlessness, tremors, fever, yawning, vomiting, lacrimation, rhinorrhea and occasionally diarrhoea appear. These general signs also reach a peak at about the same time as the hindlimb spontaneous activity, but they subside much more rapidly. The effects of sodium pentobarbital, neostigmine, eserine, and elevation of body temperature changes on the hindlimbs of chronic spinal dogs are described, and similarity of changes considered. The data are discussed with reference to the problems of loci of action of morphine and methadon, theories of physical independence, and studies of physical dependence-producing liability of drugs.

(Wikler Abraham Lexington Kentucky Senior Surgeon United States Public Health Service and Frank, Karl Biophysicist Hindlimb Reflexes of Chronic Spinal Dogs During Cycles of Addiction to Morphine and Methadon. The Journal of Pharmacology and Experimental Therapy Vol 94 No 4 p 382, December, 1948)

ERYTHROBLASTOSIS AND EXCHANGE TRANSFUSION

The method of treatment of erythroblastosis fetalis with exchange transfusion is described in a recent report, summarizing the results of 28 cases, by Weiner and Wexler. In their opinion the pathogenesis of the disease in the typical case, where the Rh-positive erythroblastosis baby is born with its red cells coated with "univalent" Rh antibodies,

derived from the mother by transplacental filtration, that in some cases, it is possible that additional Rh antibodies of the "bivalent" type (agglutinins) may be milked into the fetal circulation by the uterine contractions occurring during labor

In any event the antibodies acting on the infant's red cells may cause them to hemolyze or to clump. In cases in which only hemolysis occurs, a hemolytic anemia results which responds to simple transfusions of Rh-negative blood. Intravascular clumping, when it occurs, probably takes place to the greatest extent after birth, because in utero the conglutinin content of the fetal plasma is low. The authors believe that with the birth of the infant, the conglutinin content may rise to a concentration sufficient to cause clumping of red cells. If during the early stages of the disease the infant's blood is drained off and simultaneously replaced with type Rh blood of a compatible blood group, it is considered likely that the disease will become aborted, because type Rh blood cells cannot be clumped by the Rh antibodies in the baby's body.

All pregnant women should be screened to determine if they are Rh positive or Rh negative. Grouping and Rh Hr typing are done on the husband and all living children of those pregnant women found to be Rh negative, and information obtained, as to whether the husband, if Rh positive is homozygous or heterozygous. The husband's parents in certain instances must be tested to obtain this information. Since, when the maternal serum contains univalent Rh antibodies, the severity of the disease usually bears a direct relationship to the titer. Mildly sensitized women are delivered at term and the infant is treated expectantly and watched for the development of anemia, jaundice, or other signs of erythroblastosis.

In those cases where moderate sensitization has developed, the infant is delivered about two weeks before term and treated with immediate exchange transfusion using 500 c.c. of donor's blood for the procedure. More severely sensitized women may be delivered somewhat earlier and the infant treated by immediate exchange transfusion using about 1,000 c.c. of blood. With very high titers the fetus usually fails to survive until the period of viability, and the resultant dead fetuses are aborted or permitted to deliver spontaneously.

In the technique used by Weiner and Wexler, citrated blood is introduced into the saphenous vein at the ankle and the infant's blood simultaneously withdrawn from the radial artery at the wrist, coagulation being prevented by the administration of small amounts of heparin. The procedure besides being simple, is safe, there having been no operative mortality in more than 40 transfusions. Of the 28 cases treated, only seven of the infants died, and the available data indicate that the mortality would have been at least twice as high had the usual treatment with simple transfusion been given. Fresh blood was preferred to bank blood, because of its greater survival time and smaller likelihood of introducing infection. All infants who have survived have developed normally both physically and mentally and have shown no sequelae of brain damage.

(Weiner A. S. and Wexler I. B. Brooklyn, New York. *Blood. The Journal of Hematology, Results of Therapy of Erythroblastosis with Exchange Transfusion*, (Blood) Vol. IV, No. 1, January, 1949.)

Witelnsky E., Rubin, M. I., and Blum, I. Studies in Erythroblastosis Fetalis. I. Activation of the Incomplete Rh Antibody by the Serum of Full Term and Premature Newborn Infants. *Journal of Laboratory and Clinical Medicine* 32: 1330-1338, 1947.

Recent Developments in the Knowledge of the Rh Hr Blood Types. Tests for Rh Sensitization. *American Journal of Clinical Pathology* 16: 477-497, 1948.)

Book Reviews and Notices

PULMONARY TUBERCULOSIS Diagnosis and Treatment by S. Sen, B.Sc., M.B. (Cal.), M.R.C.P. (Lond.), F.R.F.P.S. (Glas.), D.T.M. & H. (Eng.), pp. 74 Bookland Ltd., 1, Sankar Ghose Lane, CALCUTTA 6, Price Rs. 4 8 23 x 14 cm 1949

This short essay on pulmonary tuberculosis is divided into three chapters. Chapter one deals with the diagnosis of pulmonary tuberculosis, chapter two with treatment and the third chapter is on control of tuberculosis.

Compared to many excellent works on tuberculosis that are available this book seems rather superfluous. But as stated by the author in his foreword it may prove of some value to the general practitioner for ready reference on some point about tuberculosis.

The subject is treated in a very short and sketchy manner so much so that at some places things are left over with a mere reference to the subject.

There does not seem to be any clarity about Allergy and Hypersensitivity in Tuberculosis in the author's mind, when one reads contradictory statements as on pages 23 and 74.

At many places errors of printing have crept in which could have been avoided by little care.

However the Appendices about surgery in tuberculosis, childhood tuberculosis, and the utility of Mantoux test, at the end of the book make an interesting reading.

To make it an useful book for the practitioner the author, who is a physician to the General Hospital, Rangoon, and Head of the Department of Pharmacology, should amplify it with his personal experience in Burma and with references to the literature on tuberculosis in India.

B R S

ALL-INDIA MEDICAL DIRECTORY AND WHO'S WHO 1949-Edited by K. V. Mathew, HEALTH BOOKSTALL, MADRAS Size 17 x 25 cm Pages about 600 Rs. 20/-

An accurate All-India medical directory and who is who is a much-needed reference book for all sorts of workers in India and in spite of various attempts by publishing firms and private individuals, we are still without a reliable publication. Most publications were careless, incomplete, inaccurate and methodless. We regret to note that the present publication also, though it appears with a trumpet foreword and glossy photographs of a few showmen politicians, falls in the same category. It is divided in eight sections dealing with (A) General Information, (B) Medical Education, (C) Chemists, Pharmaceutical and Surgical Dealers, (D) Dentists and Doctors, (E) Hospitals, (F) Special Institutions, (G) Medical Publishers and Booksellers, and (H) Latest advances in treatment. Mere list of names in Section F is hardly of any value, Section H makes a strange bedfellow in a medical directory.

Looking through the sections dealing with Bombay Province, one is constrained to note that it is full of inaccuracies which could have been avoided by careful editing and local check-up. One wonders why the book is titled "Who Is-Who" because except for a chosen few names there is little information about the rest except the address. We hope that better organisation, hard work and method will produce a more reliable and complete edition in 1950. Perhaps the task of production of an All-India Directory is too big for the publishers.

Original Contributions

CHLOROMYCETIN IN ENTERIC FEVER

by

RUSTOM JAL VAKIL

M D (Lond), M R C P (Lond) D T M & H, F C P S F A Sc, F R F P S
K E M Hospital BOMBAY

Numerous attempts have been made in the past to discover some therapeutic agent capable of exerting a specific bactericidal or antitoxic effect on the causative organisms of the enteric group of fevers but so far, such attempts have not been rewarded by any degree of success

Following the report of Woodward, Smadel, Ley, Green and Mankiker (1948), on the effectiveness of chloromycetin therapy in ten cases of typhoid fever at Kuala Lumpur, Malaya, it was resolved to carry out similar clinical trials in cases of typhoid fever in India. The enteric group of fevers constitute a public health problem of major importance in this country, claiming annually a very heavy toll of life, in view of such a gloomy picture, it is but natural that any new preparation or drug with any claim to therapeutic effectiveness in this group of fevers should claim our earnest attention. As far as I can ascertain, this is the first paper, published in India, on the clinical evaluation of chloromycetin in cases of enteric fever. It deals with a relatively small series of fourteen cases of typhoid and paratyphoid fever, treated with chloromycetin, in Bombay, during the past two months. The patients of the present series were hospitalised in several of the hospitals and nursing homes of Bombay. In view of the limited supplies of chloromycetin available, at the present time, in Bombay, we have had to be satisfied with this small series of cases.

Chloromycetin (Chloramphenicol, Parke Davis) is a pure crystalline substance with specific antibiotic properties. Its discovery, far from being accidental or fortuitous, has been the result of laborious investigations undertaken by several teams of distinguished scientists.

From amongst innumerable soil samples, collected from diverse regions of the universe, several thousand cultures were prepared and studied by Burkholder of Yale University. From a large number of such cultures exhibiting antibiotic propensities, Ehrlich and his associates, working at the P D Research Laboratories, were able to isolate a special variety of streptomycetes from a soil-sample obtained from a mulched field in Venezuela, hence the designation of "streptomycetes venezuelae" proposed by Ehrlich and associates. The same antibiotic substance has also been isolated (at a later date) quite independently, from a different soil-sample by Gottlieb and his associates, working at the University of Illinois.

As the result of innumerable experiments in the laboratory, chloromycetin has been shown to be effective against an extensive range of pathogenic organisms and therapeutically beneficial in rickettsial infections, typhoid and paratyphoid fevers and even in urinary infections.

Smadel and his associates of the Research and Graduate School of the Army Medical Department, were able to show that chloromycetin can be safely administered to human volunteers with no ill effects whatsoever and with rapid absorption of the drug by the gastro-intestinal tract.

Of late, several excellent clinical studies have been reported extolling the therapeutic value of chloromycetin in different types of infections. The beneficial role of chloromycetin therapy in typhoid fever was demonstrated for the first time in Malaya, by Woodward and his colleagues.

Evaluation of therapeutic benefit or cure is particularly difficult in a condition like typhoid fever, where the clinical course, duration and outcome are all so variable and unpredictable.

Clinical Material—Patients for the present investigation were hospitalised in several of the hospitals and nursing homes of Bombay. There were, in the present series, 11 cases of typhoid fever, 2 cases of paratyphoid A infection and one case of paratyphoid B. The diagnosis in each case was established either on the basis of a positive Widal test or on the basis of a positive blood culture, in some of the cases, both the Widal test and the blood culture were positive for typhoid.

The patients, of whom 11 were males and 3 females, ranged in age from 13 to 47 years, the average age for the whole series being 30.7 years. Seven of the fourteen cases were Parsees, 3 Europeans, 2 Muslims, one Hindu and one Anglo-Indian.

Chloromycetin therapy was commenced during the first week of infection in two of our cases, during the second week in six cases and during the third week or thereafter in the remaining six.

Preparation and dosage employed—The preparation employed throughout the present study was the newly discovered antibiotic chloromycetin (of Parke Davis) in capsule or "kapseal" form, each capsule containing the equivalent of 0.25 g. of the active substance. In view of the limited water solubility and the irritant properties of suspensions of chloromycetin on intramuscular injection in dogs, its parenteral application in human subjects has been deprecated by Smith and his associates. In view of this fact, all cases of the present series were subjected to the influence of the oral preparation only. In some of our cases, the scheme of dosage adopted was that recommended by Woodward and his associates, viz., an initial dose of 50 mg. per Kg. of body-weight, followed by a dose of 0.25 g. every two hours during the period of pyrexia and a subsequent dose of 0.25 g. every three or four hours for five more days. Because of limited stocks and prohibitive prices the dosage of chloromycetin had to be cut down and modified in several of our cases. For full details about the actual scheme of dosage adopted in each case, please refer to Table 1.

Results of Chloromycetin Therapy—After the onset of chloromycetin therapy, normal temperature was registered (for the first time) within 48 hours in 6 of the cases, within 72 hours in 9 of the cases and within 96 hours in as many as 11 of the cases, in other words, only 3 of the 14

cases failed to register normal levels of temperature within four days of onset of therapy (See Table I)

Persistently normal temperature (or the actual end of the pyrexial phase) was recorded within 72 hours or three days of onset of specific therapy in 3 of our cases and within 6 days of onset of therapy in as many as 10 of the cases. Of the remaining four cases, normal temperature was restored on the 12th day of therapy in one case, and on the 11th day in another case, the third case continued to run a low-grade pyrexia, ranging from 99° to 100° F, for over twenty days whilst, the fourth case, having proved quite refractory to the drug, was put on streptomycin injections

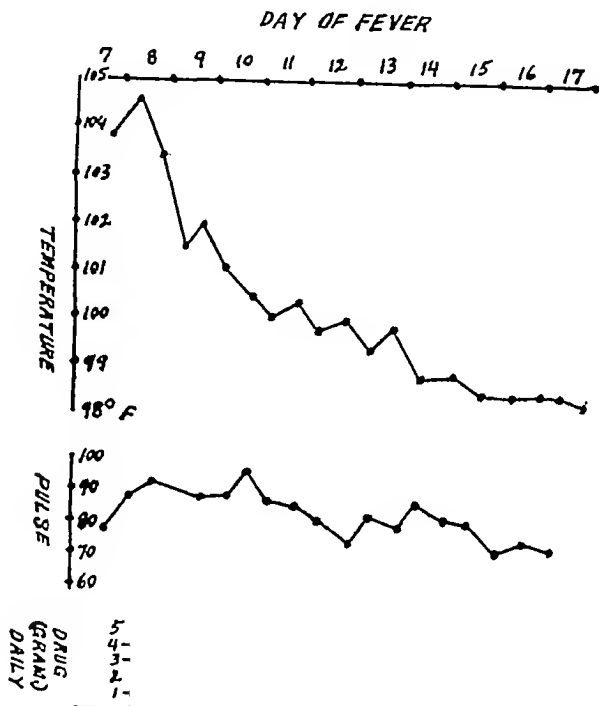


Chart 1 Typical response of a case of paratyphoid fever (case No. 2) to chloromycetin therapy. Note the drop of temperature to normal in two stages and the maintenance of a constant pulse rate in spite of decreasing temperatures. (For details see text)

Regarding the action of chloromycetin on the temperature of enteric cases, our impression, from a very limited experience of course, has been that the drug has a definitely temperature-lowering action in the great majority of cases, also, that the drop of temperature to normal levels appears to occur "in step-ladder fashion" or to be more exact, in two stages. There is a primary drop of temperature of two or more degrees during the first two or three days of onset of therapy, followed by a short or long phase of low-grade pyrexia and then, a second drop of temperature to normal levels. This drop of temperature in two stages, with a short intermediate phase of low-grade pyrexia, was observed in several of the cases (See Chart I)

Effects of chloromycetin therapy on the pulse-rate—The pulse rate chart, in the majority of cases, showed a rather peculiar although harmless behaviour during and after chloromycetin therapy. There was a tendency for the characteristic sinus bradycardia of typhoid to lessen or disappear, during therapy, in several of our cases, with the result that the pulse rate showed little or no alteration in spite of decreasing levels of temperature. For instance, in one of our cases, although the temperature level dropped from 103.2 to 98.4, the pulse rate actually rose from 74 to 78 per minute. In another case, the pulse rate which was 84 with a temperature of 103° F remained the same even after the temperature had touched normal. Excessive tachycardia was not, however, a feature of any of our cases.

Effects of chloromycetin therapy on blood counts—The red blood cell count and haemoglobin percentage could be determined, both before and after therapy, in only four of the cases. In three of these, the values remained unaltered at the end of treatment, in the fourth case, the drop in haemoglobin percentage was ascribable more to intestinal haemorrhage than to administration of the drug.

Table 2 Behaviour of the white blood cells during chloromycetin therapy.

CASE No	BEFORE THERAPY					AFTER THERAPY				
	Total W B C	Polys	Lympho	Eosin	Monos	Total	Polys	Eosin	Monos	Lympho
1	5720	40%	58%	2%	0%	8100	49%	2%	4%	45%
2	5200	02	35	3	0	4550	50	1	10	39
3	8850	73	27	0	0	3250	01	0	0	30
4	8050	00	34	0	0	2050	45	0	0	55
8	3400	40	50	2	2	5900	60	0	0	40
9	0200	00	38	2	0	4800	52	2	0	40
10	5750	50	40	2	2	4550	44	2	4	50
11	5240	52	45	1	2	4810	50	0	1	40

In the case of white blood cells, there is a definite tendency towards leucopenia after the administration of chloromycetin. This opinion of ours is shared by several of our colleagues in Bombay. Out of the eight cases of the present series, where white blood cell counts had been carried out both before and after chloromycetin therapy, a further drop in the total W B C count (ranging from 430 to 5600 cells per cmm) was observed in as many as seven of the cases. In only one case, was there a rise of W B C cells after therapy (See Table 2). A moderate reduction of white blood cells has, therefore, to be expected in the great majority of cases treated with chloromycetin. The leucopenia in most cases was of a very mild order and required no interference, in only one case (viz. case 3) did we consider it necessary to abandon the drug on the grounds of leucopenia.

A study of differential white cell counts revealed a fairly constant reduction, of a mild or moderate order, in the relative percentage of polymorphonuclear cells (See Table 2). In no cases of ours, however, did this granulocytopenic tendency attain serious proportions. The only exceptions to this rule were cases 1 and 8, where an actual increase in the proportion of polymorphonuclear cells was observed after treatment. In keeping with the relative granulocytopenia, there is usually an increase in the relative percentage of lymphocytes.

The eosinophil cells showed neither a tendency to rise nor to fall after chloromycetin therapy whilst, in the case of monocytes, there was a distinct rise in the percentage of these cells in as many as 50% of the cases investigated (See Table 2) After chloromycetin therapy there was a rise of monocytes from 0% to 10% in case 2 and a rise from 0% to 6% in case 9 Whether this preliminary observation of ours about the rise in percentage of monocytes is purely accidental or real requires further investigation

Untoward effects of chloromycetin therapy—Toxic reactions of any degree of severity were singularly few in the present series of cases Untoward effects, when observed, were essentially of a benign order and resulted neither in loss of life nor in grievous harm to the patient In our experience, the commonest side-effect of chloromycetin therapy was a tendency to excessive sweating or perspiration, this was complained of by seven of our fourteen patients and apart from the inconvenience of the symptom caused no further trouble

Apart from excessive sweating, the following were the symptoms or side-effects observed in the present series of cases, viz anorexia or loss of appetite in four cases, mild diarrhoea in three, oliguria or reduced output of urine in four, abdominal discomfort or "soreness" in two, nausea and vomiting in one, abdominal distention in one, extrasystoles in one, albuminuria and cylindruria in one, giddiness in one and excessive leucopenia in one

In two of our cases, treated on large doses of chloromycetin, electrocardiographic studies revealed no evidence, whatsoever, of any toxic effect on the myocardium or on the conducting tissues of the heart

The incidence of typhoid complications, relapses and deaths—The classical complications of typhoid were singularly few in the present series During and after chloromycetin therapy, intestinal haemorrhage only twice, cystitis once, parotitis once, hypostatic pneumonia once, jaundice once and intestinal perforation not at all

Of the fourteen cases reported here, only two displayed a second rise of fever or relapse One of our cases, however, still remains under observation for low-grade pyrexia, secondary to the primary attack

Not a single death was encountered in the present series

Summary and Conclusions—(1) A short account is presented of fourteen cases of typhoid and paratyphoid fever, observed in Bombay City and treated with chloromycetin, the new antibiotic supplied in capsule form by Parke Davis and Company

(2) On the whole, the clinical response to the drug was most satisfactory and normal levels of temperature were restored in most cases, within a few days of starting of therapy There appeared to be a material reduction in the length of pyrexia in those cases treated on chloromycetin

(3) There were no deaths or serious complications from the oral use of the preparation Apart from a few unpleasant side-effects of no consequence, there were no toxic reactions

On the basis of our limited data, we are inclined to regard the administration of chloromycetin in typhoid and paratyphoid fevers as a fairly safe measure, with clinical results encouraging enough to warrant a further and more extended trial of the new antibiotic

My sincere thanks are due to Col S Vazifdar I.M.S. M.R.C.P. (Lond) and to Dr Lenczner, M.D. for co-operation and help in the preparation of this paper

REFERENCES

- 1 BARTZ Q R Isolation and Characterization of Chloromycetin *J Biol Chem* 172 445, 1948
- 2 EDITORIAL *J 4 M A* 138 432 1948
- 3 EHRLICH J BARTZ Q R SMITH, R M W JOSLIN, D A Chloromycetin, A New Antibiotic from a Soil Actinomycete *Science*, 106 417, 1947
- 4 EHRLICH J, GOTTLIEB D, BURKHOLDER P R ANDERSON L E and FRIDHAM, T G : Streptomyces Venezuelae, N Sp the Source of Chloromycetin, *J Bact* 56 487 1948
- 5 GOTTLIEB, D BHATTACHARYA P K ANDERSON H W and CARTER H E Some Properties of an Antibiotic obtained from a Species of Streptomyces *J Bact* 55: 409 1948
- 6 LEY, H L Jr SMADEL J E and CROCKER T A Administration of Chloromycetin to Normal Human Subjects *Proc Soc Exper Biol w Med* 68: 9 1948
- 7 PAYNE E H KNAUDT J A and PALACIOS S Treatment of Epidemic Typhus with Chloromycetin *J Trop Med w Hyg* 51 68 1948
- 8 PAYNE E H, SHARP E A and KNAUDT J A Treatment of Epidemic Typhus with Chloromycetin *Tr Roy Soc Trop Med w Hyg* 42: 163 1948
- 9 PINCOFFS M C GUY E C LISTEN, L M WOODWARD, T E and SMADEL J E The Treatment of Rocky Mountain Spotted Fever with Chloromycetin *Ann Int Med* 29: 656, 1948
- 10 SMADEL J E and JACKSON F B Chloromycetin An Antibiotic with Chemotherapeutic Activity in Experimental Rickettsial and Viral Infections *Science* 806 418 1947
- 11 SMADEL, J E and JACKSON F B Effect of Chloromycetin on Experimental Infection with Psittacosis and Lymphogranuloma Venereum Viruses *Proc Soc Exper Biol & Med* 67 478 1948
- 12 SMADEL, J E LEON A P LEY H L and VARELA C Chloromycetin in the Treatment of Patients with Typhus Fever *Pro Soc Biol w Med* 68 12 1948
- 13 SMADEL J E WOODWARD T E LEY JR H I PHILLIP C B TRAUB R LEWTHWAITE, R and SAVOOR S R Chloromycetin in the Treatment of Scrub Typhus *Science* 198 160 1948
- 14 SMITH R M JOSLIN D A GRUNZIT O M MCLEAN I W JR PENNER M A and EHRLICH J Chloromycetin Biological Studies *J Bact* 55 425 1948
- 15 WOODWARD T E SMADEL J E LEY JR, H L GREEN R and MANKIKAR D S Beneficial Effect of Chloromycetin in the Treatment of Typhoid Fever *Ann Int Med* 29 181, 1948

CHLOROMYCETIN IN TYPHOID FEVER*

by

M J SHAH,

M B B S, M R C S (Eng), M R C P (Lond), D T M & H (Lond)

K E M Hospital BOMBAY

Any therapeutic agent promising to be effective in the treatment of typhoid fever would be of great importance to us, in the City of Bombay. Cases of enteric fever are met with all the year round in an endemic form, with seasonal epidemic waves during months of June, July, September, October and November.

The following are figures of enteric cases admitted in Sir Hurler's Hospital. It may be noted that usually the toxic and the serious cases seek admission in the hospital. A large number of cases seek admission after the onset of some serious complications such as haemorrhage, perforation, circulatory failure etc. The mortality figures include all such cases.

TABLE 1

Year	Total Medical Cases	Typhoid Cases	Percent	Total	Mortality Percent
1932	424	54	12.7	5	0.2
1937	1044	100	15.0	25	15.0
1942	1558	197	12.6	32	16.2
1947	2286	637	27.8	107	15.2
1948	2802	802	34.8	112	13.8

Historical —A new antibiotic was obtained from culture filtrates of a new strain of *Streptomyces*, originally cultured from soil by Burkholder in 1946. On its further concentration and purification an active and pure crystalline material was prepared and named Chloromycetin. Ehrlich and his colleagues studied the antibiotic properties of Chloromycetin in 1947. In vitro it was found that the culture and the crystalline agent showed marked effect against a variety of gram-negative bacilli, moderate effect against *Mycobacterium tuberculosis* and a few gram-positive cocci. On animal experimental studies, on embryonated eggs and on mice, infected with a variety of *Rickettsia* agents Smadel and his colleagues observed marked effectiveness of Chloromycetin. It was also shown to be effective against viruses of psittacosis and lymphogranuloma venereum. Clinical tests on human infections showed profound effectiveness in cases of epidemic typhus and scrub typhus. Clinical trials with encouraging and beneficial results in 10 cases of typhoid fever in Malaya were published as a preliminary report by Woodward and his associates in 1948. Chloromycetin has been available in Bombay since April 1949.

Properties —Chloromycetin is a crystalline material, neutral in reaction and containing both nitrogen and non-ionic chlorine. It is not affected by boiling in distilled water for 5 hours. It is stable in an

* A paper read at the 93rd meeting of the Seth G. S. Medical College and K. E. M. Hospital Staff Society, held on Saturday, the 11th June 1949, with Dr. A. Hamid in chair.

aqueous solution for more than 24 hours in a wide range of PH 2 to 9. It is readily, and well absorbed from the alimentary tract appearing rapidly in blood in an effective blood concentration. The elimination from the blood is also rapid, necessitating administration of frequent doses in order to maintain the effective blood levels of the drug. Of the drug eliminated from blood, only about ten per cent can be obtained from urine. The fate of the rest of the drug is not known.

The reported toxic effects are nil. In experimental animals, no toxicity was noted on injecting a dose of 100 mgms per kgm of body weight, or on larger oral dosage. No toxic effects were also noted on healthy physicians, who acted as volunteers.

The organisms mainly inhibited by Chloromycetin are *Brucella abortus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Mycobacterium tuberculosis*, *Salmonella schottenmulleri*, *Shiga paratyphosae* (Sonne), *Staphylococcus aureus*, *Rickettsia* and *Eberthella typhosa*. It is observed that *E. typhosa* is inhibited by Chloromycetin in a blood concentration of about one-quarter gamma per c c.

Material.—With the availability of the drug in Bombay from April 1949, an opportunity for clinical trials of Chloromycetin in cases of typhoid fever was presented. Advantage of the availability of the drug was taken to study its efficacy on cases of typhoid fever at Sir Harkisondas Hospital and in private practice. The cost of the drug was borne by the patients themselves in the paying wards, and from external voluntary donations for patients in the general ward of the hospital. Up-to date 26 cases have been treated in the institution. The present report also contained 7 cases treated in private, at the patients' homes. Of the total of 33 cases 12 were cases giving history of fever of 10 days or less, and 18 cases were during later period, 3 cases were with some complications before the start of treatment.

TABLE 2

Pyrexia of 10 days or less	12 cases
Pyrexia over 10 days	18 cases
Typhoid with complications	3 cases
Total cases	33 cases

The significance of the above tabulation of typhoid cases is discussed later on.

The diagnosis of typhoid fever was made on clinical grounds, and was confirmed by laboratory findings in the majority of cases.

TABLE 3

Clinical diagnosis	33 cases
Blood culture positive	8 cases
Widal positive	18 cases
Leucopenia with relative neutropenia	5 cases
No laboratory data	2 cases

Management.—The general nursing treatment and the dietetic treatment was prescribed according to the usual practice of the physician in-charge. Symptomatic relief of some troublesome symptom was given as required.

Chloromycetin was given in recommended standard dose i.e., an initial dose of approximately 50 mgms per Kgm of body-weight and a

maintenance dose of 0.25 gm (one capsule), every 2 hours till temperature was normal, to be followed by a gradual reduction of the drug over a period of 3 to 6 days, was administered in 20 cases. In other 3 cases the initial large dose was omitted, but the maintenance dose was kept as above. In 10 cases a modified dose was followed. The modification consisted in omitting large initial dose, but giving a double routine dose e.g. 0.5 gm, (2 capsules) every 2 hours till temperature touched normal, then making it 0.5 gm 4 hourly and gradually reducing it.

All the patients swallowed the capsules containing Chloromycetin, except two patients who were in coma. They were given the drug by dissolving the contents in nasal feeds every 2 hours.

A record of temperature, pulse and respiration every 2 hours and of daily fluid intake and output was kept in all the hospital cases. Repeated examinations of urine and blood count were not done in all cases, but in a few cases where it was done, no significant changes were recorded.

Blood level studies of the drug were not done.

The average total dose of Chloromycetin given in this series was 21 gms, the smallest curative dose being 6.75 gms, and the largest 85.5 gms. The average dose in cases where the recommended routine was followed was 18 gms, and in the modified routine the average was 24 gms.

Recovery was noted in 25 cases, relapse in 4 cases and death in 4 cases.

Response—The response to the drug was as follows. Out of 25 cases that recovered the temperature came down to normal and remained normal by lysis in 17 cases, by crisis in 4 cases and by pseudocrisis in 1 case. A sudden collapse was noted in 3 cases.

TABLE 4

Response	No of cases	Per cent
Lysis	17	68
Crisis	4	16
Pseudocrisis	1	4
Collapse	3	12

The table 5 shows the response in relation to hours. It was noted that in the majority of cases the temperature came down to normal in 72 to 96 hours.

TABLE 5

Time in which temperature fell to normal

Hours	24	48	72	96	Over 96	Total
Cases	3	3	9	9	1	25

Relapse was noted in 4 instances, in all of which there was an initial response by lysis, followed by a rise of temperature. In 3 cases, the relapse occurred during the period when the patients were having the drug in maintenance doses. In 1 case the relapse occurred after an afebrile period of nine days.

In three of these relapsed cases Chloromycetin was administered again in suggested standard dosage. In one of these cases it had to be stopped, because of severe bilious vomiting and diarrhoea. In the second case there was a good initial response, followed by a second relapse during the course of Chloromycetin. The third case has shown recovery by lysis, and is now afebrile for two weeks. In the fourth instance of relapse, the patient refused to take the drug.

Deaths—Four deaths were recorded in the series. One case died of progressive and increasing tympanitis during Chloromycetin therapy. Before death he was given 23 gms. of Chloromycetin with no favourable response to pyrexia or general toxæmia.

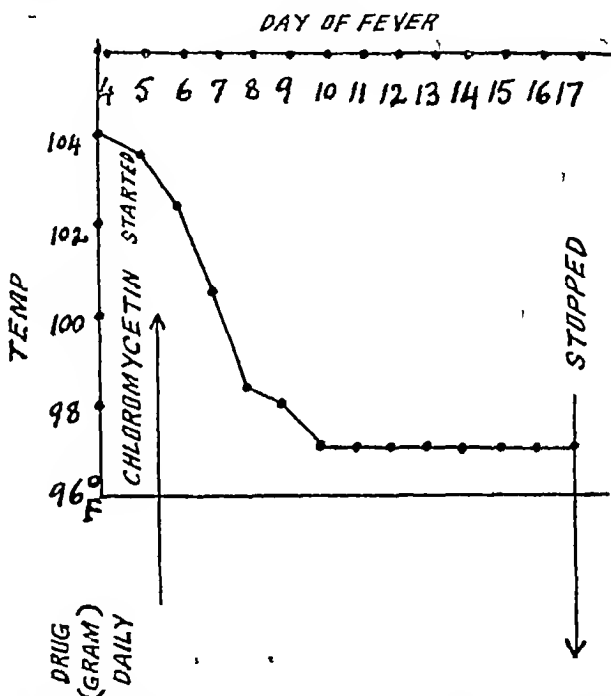


Chart 1 Case 1 R, male age 11 Continuous fever, 5 days pain in abdomen 4 days, vomiting 2 days. Blood culture positive for *E. typhosus*. Widal negative. Blood R B C 3.0 ml, W B C 4800. Polys 76 Lymphs 20 Mono 4 per cent. Chloromycetin initial dose 1 gm, maintenance 0.25 gm 2 hourly. Total amount 21 gm. Temperature came down by lysis in 60 hours. No complications. No toxic effects.

The second patient became afebrile in 48 hours. Chloromycetin was continued in maintenance doses. On the 3rd day of afebrile period (i.e. 5th day of Chloromycetin), the patient got convulsions, collapsed and died in few hours.

The third case was associated with typhoid osteomyelitis of the occipital bone. He was treated by a course of Chloromycetin, Penicillin and Streptomycin, with no response. He showed evidence of increasing intracranial tension. Surgical treatment—trephining and tapping the lateral ventricles—was done. He died in 48 hours after surgical treatment.

The fourth was a case of suspected perforation, where the relatives refused surgical treatment. The child was treated by combined Chlo-

romycetin, Penicillin and Streptomycin Blood transfusions, glucose-saline infusions and other supportive measures were followed The child expired on the fourth day of Chloromycetin

Even if the last case of the perforation is discarded 3 cases out of 33, died giving the mortality of 9.1% The series is too small to consider the percentage of mortality as compared to previous years

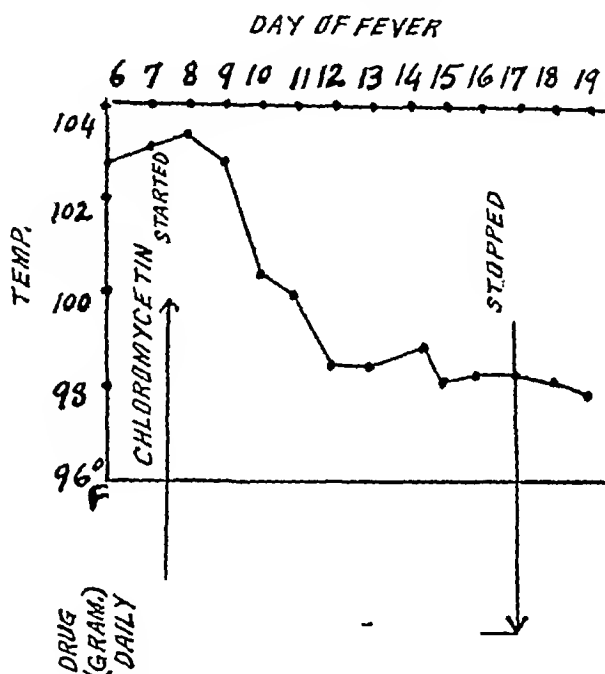


Chart 2 Case 4 V P, male aged 21 Continuous fever headache constipation 7 days Blood culture positive for *E. typhosus* Widal positive for H 1 in 125 for O 1 in 50 Blood R B C 4.1 mil Hb 80 per cent W B C 4500 Polys 68 Lymphos 32 Monos 2 per cent Chloromycetin initial dose 1.5 gm maintenance dose 0.25 gm 2 hourly Total amount 19.75 gm Temperature settled down by 12 hrs in 96 hours The patient had delirium, restlessness bilious vomiting diarrhoea, profuse sweating and rash

Results in 8 cases of typhoid fever with positive blood culture showed recovery in 7 cases, relapse in 1 case and no death

TABLE 6
Results in 8 cases with positive blood culture

	Cases	Expired	Relapsed but recovered later with II course of treatment	Recovered	Average time in hours for response	Average total dose
Pyrexia of 10 days or less	6	Nil	Nil	0	78	18 Gms
Pyrexia over 10 days	2	Nil	1	1	00	21 Gms
Total	8	Nil	1	7		

Therapeutic response of the drug as related to the duration of disease at the start of treatment is shown in the next table. It was noted that in the 12 cases of pyrexia upto first 10 days, there was recovery in all cases. No relapse and no death were recorded.

TABLE 7

	Total	Recovery	Relapse	Death
Pyrexia upto 10 days	12	12	Nil	Nil
Pyrexia over 10 days	18	12	4	2
Complications	3	1	Nil	2

Toxic effects —The following side effects were noted. The symptoms that manifested after the initial dose or during the maintenance dose of Chloromycetin were noted as toxic symptoms of the drug. The toxic symptoms as recorded are shown in the next table. One, two or more toxic symptoms occurred in some cases.

TABLE 8

Toxic effects	Pyrexia under 10 days	Pyrexia over 10 days	Total
Nausea and vomiting	1	0	7
Diarrhoea	8	4	7
Distension	1	6	7
Urinary Retention	2	5	7
Circulatory failure (collapse)	2	2	4
Cerebral irritation	3	4	7
Stomatitis		1	1
Blurring of vision (transient)		1	1
Erythematous rash		1	1

It was noted that the toxic symptoms were noticed both in early cases of pyrexia upto 10 days and in later cases. In few cases where the drug had to be stopped, the observed toxic symptoms gradually disappeared.

DISCUSSION

(a) *Is Chloromycetin effective in typhoid fever?*

There is no question that to-day Chloromycetin is the most effective known agent for therapeutic use in cases of typhoid fever. Experimental studies have shown that Chloromycetin inhibits the growth of *Eberthella typhosa*. In the present series of 33 cases of typhoid fever 25 cases recovered and 4 relapsed. But in 12 cases of typhoid fever of less than 10 days duration all recovered. Complete recovery in seven cases and relapse in one case was noted in the 8 cases diagnosed as typhoid and confirmed by a positive blood culture. Besides controlling the temperature by lysis in majority of cases, the drug also controls the typhoid toxic state. The effect on the toxic state seems to be slower than on the fever. Relapse was noted in four instances, in three of which the relapse occurred during the drug therapy. In four cases that expired, one was a case of suspected perforation (prior to treatment),

X 1461	M	7	50	+	4900 P 64 L 36	29	1	0 25 Q2H	25	10	Lysis in 140 hrs	Expired (Had also typhoid osteomyelitis skull as seen in skin grams Lateral ventri- cles were tapped & penicillin & strepto- mycin were also given
XI 1816	M	6	30		2900 P 78 L 20 E 2	16		0 25 Q2H	9	3	Nil	Expired A case of typhoid perforation Operation refused Treated by Chloromy- cetin, Penicillin Strepto- mycin Blood trans- fusion Intestinal suc- tion
XII 1634	M	28	100	+	5100 P 54 L 46	33	2	0 25 Q2H	24	10	Lysis in 68 hours	Recovered
XIII 2125	F	10	40	+	7000 P 70 L 30	23	75	0 25 Q2H	10	7	Lysis in 40 hours	Recovered (Patient had parotitis which subsided in 2 days of Chloromycetin treat- ment)
XIV	M	30	120	+		30	2	0 25 Q2H	17	5	Nil	Recovered but there was no response to Chloromycetin & hence the drug was discon- tinued
XV	M	8	40	+		10		0 5 Q2H	6 75	30 hrs	Collapse in 30 hrs	Recovered (Treat- ment was incomplete but no fever after stop- ping the treatment, urine Mental ping the confusion
XVI 2310	M	18	120		2750 P 56 L 44	10	2	0 25 Q2H	21	9	Lysis in 84 hours	Recovered
XVII	M	25	100	+		12	1 5	0 25 Q2H	21	10	Lysis in 6 hours	Recovered
											Diarrhea abdominal distension	

one of typhoid osteomyelitis of occipital bone associated with increased cerebral pressure, one died of increasing abdominal distension during chloromycetin therapy, and the fourth died of convulsive fits and circulatory collapse during the maintenance treatment after the fever was controlled. Probable toxic effects of varying grades e.g. nausea, vomiting, diarrhoea, distension, retention of urine, acute circulatory failure, delirium, and fits were noted in a few cases.

The conclusion regarding the therapeutic value of Chloromycetin in typhoid fever, drawn from the present study is that the results are very encouraging if used early, before the 10th day in typhoid fever, but not convincingly ideal, though quite encouraging, for later cases and for complications.

(b) *What would be the best time in the course of typhoid fever for Chloromycetin therapy?*

In the present series 12 cases of duration of illness under 10 days showed recovery in all cases. This finding is significant.

In typhoid fever, during first nine or ten days, there is only swelling of lymph follicles and Peyer's patches in small intestine. The toxic effects on various viscera are usually not marked. If the typhoid bacilli are successfully attacked during this period, swollen lymphoid tissue will undergo resolution. There will be no slough formation, no ulcer formation due to separation of sloughs, and no risk of complications like hæmorrhage or perforation. In order to achieve the objective, the following routine was adopted by me. In cases of fever of less than 10 days duration, if a clinical diagnosis of enteric fever was made, an immediate request was made to the pathology department for taking the patient's blood for blood culture, Widal test and blood count. After the blood was taken the patient was put on Chloromycetin. In event of negative laboratory reports, the blood was again examined at a later date. In majority of cases, positive laboratory findings confirmed the clinical diagnosis.

Administration of Chloromycetin after the tenth day of fever would control the fever. But the risks of hæmorrhage, perforation, diarrhoea, distension and other complications would remain because of sloughing and ulcerations that would occur in typhoid. In the present series 18 cases were given Chloromycetin after the tenth day of fever. Of these 12 recovered, 4 relapsed and 2 expired.

Presentation of Chloromycetin after the onset of serious complications e.g., hæmorrhage, perforation, cannot help the local lesion, but may prove of indirect value by control of fever and toxæmia. One case of perforation was treated with no benefit.

(c) *Are there toxic effects of Chloromycetin?*

It is a very difficult question to answer at present. The toxic effects e.g. vomiting, diarrhoea, retention of urine, sudden circulatory failure and cerebral symptoms noted in the present series, are known to occur during the course of typhoid fever. But as pointed out previously the symptoms that appeared after and during the administration of chloromycetin were recorded as toxic. At present the reported symptoms should be considered as probable toxic symptoms in view of the fact that the drug has been reported to be non-toxic to experimental animals and to human volunteers. No toxic effects were reported in cases of Typhus fever treated by Smadel, and in cases of Typhoid fever

by Woodward In spite of these reports one is inclined to believe that Chloromycetin does produce toxic symptoms of varying grades, as noted in the present study

Economic aspects—The cost of the drug in Bombay at present is high and prohibitive to a large number of middle class and poor patients, who form the great bulk of typhoid cases The cost becomes more apparent, if it is viewed from the point of availability of dollars for the import of the drug Let it be hoped that in very near future the cost of the drug will come down to a level at which even the poor can afford to buy (At present a patient on an average needs 21 gms of Chloromycetin, which costs approximately 400 rupees)

Dose What should be the dosage and the frequency of administration of Chloromycetin ?

Chloromycetin rapidly appears in blood because of quick absorption from alimentary tract Elimination from blood is also rapid Smadel and his associates who studied the effect in physician volunteers found that after administration of a single dose of 2 gms appreciable amount of the drug was present in 30 minutes both in blood and urine No drug was present in blood at the end of eight hours It was further noted that with an initial dose of 1 gm followed by 0.2 gm doses every four hourly, the drug could be maintained at an effective blood level

Woodward and his associates treated 10 cases of typhoid fever by an initial dose of 50 mgms per Kg. of body-weight, followed by a maintenance dose of 0.25 gm every two hours till the fever came down

In the present series 20 cases are treated according to the dosage recommended by Woodward, and 10 cases by a modified method as described above In the first group of 20 cases the average total dose was 18 gms, toxic effects of varying grades were noted in 12 cases, and recovery occurred in 17 cases In the second group of modification of dosage in 10 cases, the average total dose was 24 gms toxic effects were noted in 5 cases, and recovery occurred in 9 cases Blood level studies of the drug were not done in any case The average cost to the patient is increased in the second group

The data in the present study are insufficient to arrive at any definite conclusions regarding the dosage and the frequency of administration

Conclusions and Summary

- 1 Chloromycetin was used in 38 cases of typhoid fever Recovery followed in 25 cases, relapse in four cases and death in four cases
- 2 In 12 cases Chloromycetin was used within 10 days of typhoid fever All cases recovered No relapse and no death occurred in this series
- 3 The fever came down by lysis in 72 to 96 hours in nearly two-thirds of the cases In others the fever came down by crisis, pseudo-crisis, or even with collapse
- 4 Average total dose of Chloromycetin used was 21 Gms A dose of 18 Gms to 24 Gms was needed in majority of cases
- 5 Toxic symptoms (e.g. nausea, vomiting, distension, diarrhoea, retention of urine, delirium, convulsions, rash and stomatitis) of varying grades and severity were noted in nearly half the cases

REFERENCES

- 1 BURKHOLDER, P R, EHRLICH J, BARTY Q R, SMITH, R M, and JOSLYN, D A, Chloromycetin a new antibiotic from a soil actinomycete, *Science*, 1947 Cvi, 417
 - 2 EHRLICH J, SMITH R M, JOSLYN, D A, GRUNZIT O M, MCLEAN I W, JR, and PENNER M A Chloromycetin biological studies, *Jr Bact* 1948 Iv 425-447
 - 3 SMADEL, J E and JACKSON E B Chloromycetin, an antibiotic with Chemotherapeutic activity in experimental rickettsial and virus infections *Science* 1947 Cvi, 418
 - 4 SMADEL J E, LEON H E, LEY, H L, JR and VARELA, G Chloromycetin in the treatment of patients with typhus fever, *Pro Soc Exper Biol and Med*
 - 5 WOODWARD SMADEL, LEY JR, GREEN and MANKIKAR Chloromycetin Preliminary report on the beneficial effect of Chloromycetin in the treatment of typhoid fever *Annals of Internal Medicine*, July, 29 131-135
-

Clinical Case Reports

REPETITIVE AURICULAR PAROXYSMAL TACHYCARDIA FOLLOWING PROSTATECTOMY

by

V V SHAH, M D, M.R.C.P (LOND.), M.R.C.P.E

Topicala National Medical College and Nair Hospital, BOMBAY

In Paroxysmal Tachycardia there are sudden attacks of extreme acceleration of the heart rate that last from a few seconds to a few days and have an abrupt onset and offset. Apart from paroxysmal auricular fibrillation and flutter, simple paroxysmal tachycardia is either auricular, ventricular or rarely nodal, depending upon the site of excitation which is outside the sino-auricular node. In the average patient with paroxysmal tachycardia, often the patient is not seen during an attack and one has to rely for diagnosis on the typical history of rapid palpitation having a sudden beginning and sudden termination. Parkinson and Papp (1947) have described a special variety of paroxysmal tachycardia, in which short paroxysms separated by sinus beats constantly recur over months or years and in which recurrent paroxysms are the rule and normal rhythm is the exception. I have used the word repetitive in its literary sense and in the case described here the repetitive paroxysmal tachycardia is an incident and normal rhythm is the rule.

L A, male aged 60, an accountant, had increased frequency of micturition for three months. During this period, he developed acute retention of urine twice which was relieved by catheter drainage. Catheterisation was followed by profuse hæmaturia. His blood pressure was systolic diastolic 180/120 mm Hg. A supra-pubic drainage was carried out. One month later, his blood urea was 21 mg per 100 ml. Urea concentration test showed less than 1.5 per cent of urea in all samples. His B.P. was S/D 180/80 mm Hg. The size of his heart was both clinically and radiologically normal. There was a systolic murmur at aortic area and 2nd aortic sound was accentuated. Brachial arteries were tortuous and thickened. Fundus showed arteriosclerotic retinopathy. There were no hæmorrhages or exudates and the disk was normal. There was no cardiographic evidence of myocardial damage or left ventricular hypertrophy. Radioscopy showed generalised dilatation of aorta due to atherosclerosis. Blood Kahn was negative. A suprapubic prostatectomy was carried out on 11th of February. Prostate was shelled out easily but hæmorrhage was severe and the packing had to be resorted to. Blood transfusion 400 ml was given. Nine hours later he had symptoms and signs of acute dilatation of stomach which were promptly relieved by gastric lavage and continuous gastric suction. Next morning there was no distention and patient was comfortable. B.P. was S/D 160/100 mm Hg. At 9 a.m. he had sudden feeling of discomfort in præcordium and pulse which was 90 per minute shot up to about 200 per minute. It was irregular. He was put on digoxin. His condition was getting worse, pulse continuing at about the same rapid rate for about 36 hours. On careful palpation it was found that though pulse was irregular, there were short runs of regular beats with irregularity in between. His B.P. was S/D 100/60 mm Hg and temperature 100°F.

His hands and feet were cold. Symptoms and signs of congestive cardiac failure were absent. Electrocardiogram showed auricular (supra-ventricular) paroxysmal tachycardia, each paroxysm continuing for a few seconds interrupted suddenly by a beat or two of sinus rhythm, followed by repetitive paroxysms of tachycardia. Carotid sinus pressure was not effective in terminating the paroxysm. It was felt that something was acting as an exciting factor and as there was sepsis in the bladder brought on by disintegrating blood clots and incomplete drainage, predisposing the patient to uraemia, the packing in the bladder was removed and the bladder was irrigated. Very soon the pulse dropped to about 120 per minute (sinus tachycardia) and by the evening settled

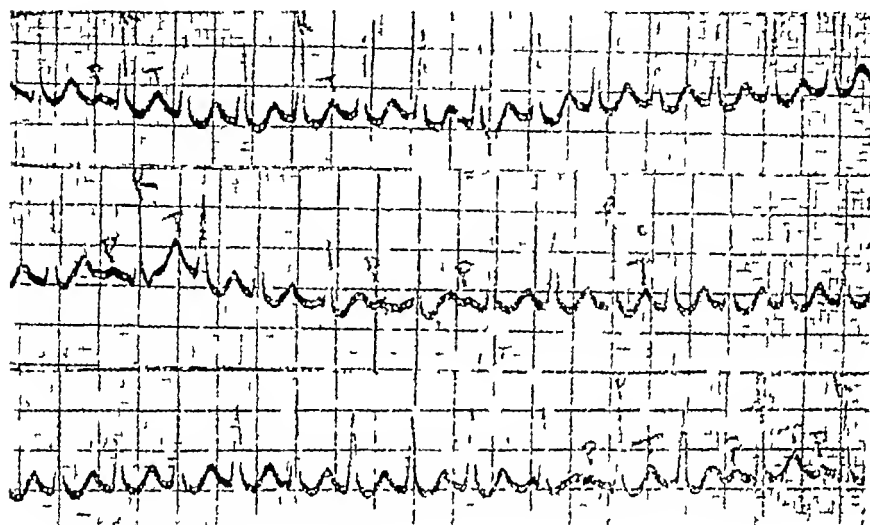


Fig 1 Lead II showing repetitive Auricular Paroxysmal Tachycardia, rate 200 per min

down to 90 per minute, with temperature also coming to normal. As the attack subsided, vagal stimulants and quinidine were not required to be given. His further progress was uneventful and to date, there has been no recurrence of paroxysmal tachycardia.

Comments—Clinically three possibilities arise, viz, repetitive paroxysmal tachycardia, auricular flutter with varying grades of heart block and rapid auricular fibrillation. It may be pointed out that in ventricular paroxysmal tachycardia, slight irregularities are not uncommonly found in contrast to auricular paroxysmal tachycardia, in which the rhythm is perfectly regular. A cardiogram is essential in deciding the diagnosis.

Many attacks of paroxysmal tachycardia start for no apparent reason and without any warning. Sometimes the patient knows the usual exciting factor e.g. sudden movements such as stooping, turning on one side, jumping and running upstairs, emotional upsets, anxiety about the supposed gravity of the illness, flatulent dyspepsia etc. Such history is far too common to be due to chance though often no cause can be detected. In this case there was no organic disease of the heart and the cardiogram did not reveal myocardial damage. Absence of previous

history of similar attacks of paroxysmal tachycardia, during his long life of sixty six years (patient being a good witness), absence of response to vagal stimulation (carotid sinus pressure etc.), irregularly repetitive nature of auricular paroxysmal tachycardia, continuance of the same state for about 36 hours, and absence of recurrence after removal of packing with free drainage and bladder irrigation are points which in my opinion suggest that bladder sepsis with inefficient drainage, in a patient with impaired renal function, are likely factors in acting as a trigger in setting off and maintaining this irregularly repetitive auricular paroxysmal tachycardia.

Auricular paroxysmal tachycardia occurs for the most part in an individual who has structurally a normal heart. But they are liable to have recurrence of attacks off and on throughout life, causing a great deal of discomfort and concern. It generally does not shorten life but there may be much crippling if the paroxysms are long or frequent. Prognosis in present case is good as there is no recurrence of attack so far and is not expected in absence of an exciting cause. Occurrence of this attack does not denote heart disease. It merely denotes a functional disturbance and carries an excellent prognosis.

This case also illustrates a common clinical observation that blood pressure falls and resumes a steady level after prostatectomy, following the relief of long continued retention of urine. Prostatectomy is indicated even in the presence of hypertension provided renal function is good.

(My thanks are due to Dr. S. Patrao for allowing me the use of his case notes.)

REFERENCE

PARKINSON J and PAPP C (1947) *Brit Heart J* 4: 241

VENTRICULAR PAROXYSMAL TACHYCARDIA

LASTING FOR OVER SEVEN DAYS

by

N. D. PATEL, M.D. (Lond.) M.R.C.P. (Lond.) F.C.P.S.

G. S. Medical College and K. E. M. Hospital BOMBAY

R. G. a farmer of Donbiville aged 60, while working on his farm on January 18, 1949 felt dizzy and fell down unconscious. When recovered he walked up to his house with difficulty. He complained of palpitations, breathlessness, and pain in the chest and abdomen. There was no vomiting or sweating. He was brought to Bombay and admitted in a surgical nursing home where I saw him at 9 p.m. the same day.

The patient was acutely ill, anxious, sitting up in bed, very breathless and a little cyanotic. The neck and arm veins were engorged, there was oedema of legs, the liver was enlarged and tender, about 5 inches from the costal margin. There was evidence of free fluid in the abdomen and both bases of the lungs were dull, suggesting the presence of effusion. The area of cardiac dullness was greatly enlarged, the impulse and the left border being in the anterior axillary line. The pulse was regular and the rate was about 200 per minute. The heart sounds were feeble, the first sound at the apex varied.

and at times appeared to be reduplicated. There was no murmur. The blood pressure was 100 mm Hg systolic and 75 mm Hg diastolic. The patient was obviously suffering from severe congestive cardiac failure, and the rapid regular heart rate suggested paroxysmal tachycardia. The past history was negative, he had no attacks of precordial pain or palpitations in the past, no diabetes or hypertension, or syphilis. He was put on ammonium chloride, phenobarbitone and digoxin. An electrocardiogram to elucidate the nature of the tachycardia, and to decide whether he had myocardial infarction was advised. As it

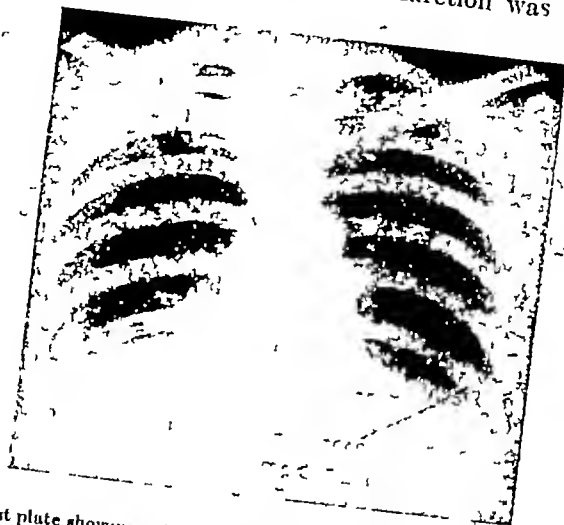


Fig. 3.—Chest plate showing enlarged heart and bilateral pleural effusions during the attack of paroxysmal tachycardia.

was not possible to do this in the nursing home, he was removed to the K E M Hospital on January 20. Unfortunately even there an immediate electrocardiographic examination was not possible. An x-ray plate taken next day showed the presence of bilateral pleural effusions and an enlarged heart (Fig 3). The electrocardiogram taken on January 22, showed the presence of a regular ventricular tachycardia, with wide bizarre QRS waves, and a rate of 220 per minute, (Fig 1). As quinidine sulphate was not immediately available the usual treatment for congestive failure was continued till January 25, when quinidine sulphate was given orally, initial dose 0.2 G, then 0.4 G four hourly. After the third dose his pulse rate fell to 110 per minute (sinus tachycardia) and next day it was down to 80 per minute. Concurrently with the reversion to normal sinus rhythm the heart size became normal, his congestion began to improve, and in the space of a few hours the peripheral oedema, ascitis and pleural effusions disappeared (see Fig 4) and the liver became normal. The patient felt so well that he requested for discharge from the hospital. The E C G taken on January 26 showed a normal rhythm, with rate of 80 and flat T waves in all leads and low voltage (from post-paroxysmal fatigue). Fig 2 shows the e c g taken on January 31, which was identical with the one obtained on January 26, showing normal rhythm, rate of 80 per minute and flat T waves suggestive of diffuse myocardial fibrosis.



Fig.1. E.C.G. on 22-1-49



Fig.2. E.C.G. on 31-1-49

As he remained quite well, he was discharged on Feb 14, an e c g taken on February 12 being similar to the previous e c g

Paroxysmal ventricular tachycardia is a serious form of arrhythmia generally occurring in the presence of grave myocardial disease or some toxic state e g digitalis poisoning. Sometimes it occurs as a functional disorder in otherwise normal persons as in the present case, where the paroxysm lasted for over seven days, from January 18 to January 25,

and when it disappeared the heart and the patient were left none the worse for it.



Fig 4 —Chest plate showing normal heart shadow and disappearance of pleural effusions, next day after reversion to normal rhythm following administration of quinidine sulphate

When ventricular tachycardia occurs in cases of coronary occlusion or myocardial infarction it is always of grave import. *It is really an emergency because the next stage is often ventricular flutter, fibrillation and death.* Slight irregularities in the rhythm, and some alterations in the heart sounds, especially in the first sound, (variation in intensity and reduplication) help to make the diagnosis at the bedside and to differentiate the disorder from auricular paroxysmal tachycardia which is absolutely regular. Even in an e.c.g. it may be difficult to differentiate the condition from auricular paroxysmal tachycardia in the presence of a bundle branch block. Vagal stimulation has no effect on ventricular tachycardia, in fact, it is dangerous and likely to induce ventricular flutter or fibrillation. Digitalis is similarly valueless, and sometimes harmful. The drug which is almost specific is quinidine. It may be given by mouth, after a test dose of 0.2 G, 0.4 G may be given every four hours till the paroxysm disappears, and then, 0.2 to 0.4 G twice a day as a prophylactic for several weeks or months if necessary. In extreme emergency quinidine sulphate may be given intravenously, 0.2 G dissolved in 25 ml of normal saline, and injected very slowly. *The procedure is not free from danger, causing a sudden cardiac arrest, with convulsions and death.* Personally I have had no occasion to use it at all. Quinidine with urea or quinidine lactate may be given intramuscularly, 0.2 G every 3 hours, till the rhythm is normal, and is said to be safer.

Critical Notes and Abstracts

ENDOCRINE ASPECT OF MALIGNANT TUMORS by
GRAY H. SWOMBLA, M.D. (*Ohio State Medical Journal*, October 1948,
44: 1009-1012)

Perhaps one of the most significant advances in our present day conception of cancer is the realization that certain malignant tumors may be made to regress by various changes brought about in the physiology of the patient's body. Agents causing local tissue removal or destruction are still our principal methods of permanent cure. We now believe, however, that it may ultimately be possible to bring about permanent regression of cancer by changing the hormone balance in the patient's body.

We have treated 34 cases of cancer of the prostate primarily by orchiectomy. Of these, 29 are dead, 4 are alive after 5 years or more, and one patient was lost track of at the end of 4 years. The average duration of life after orchiectomy, in our series, was 18 months.

We believe that while orchiectomy or stilbestrol therapy may produce few definitive cures of carcinoma of the prostate, they do cause remarkable temporary changes in a large proportion of such cases. These changes are frequently demonstrable by physical or X-ray examination, and are not confined to subjective symptoms, which of course are notoriously unreliable.

In cancer of the breast, it had been shown that about 28% of bone metastases will respond to testosterone therapy, at least temporarily. Metastases to other sites do not seem to respond so favourably, and the primary cancer does not respond at all. The use of stilbestrol in carcinoma of the breast produces favourable results in women past the menopause, whereas in young women with breast cancer there appears to be a stimulation rather than a depression of the growth rate.

In young women with breast cancer, surgical or radiation castration may produce unequivocal evidence of the healing of bony metastases.

Castration has been tried in cases of cancer of the male breast. About half the cases so treated show definite improvement, and the cancer so controlled remains inactive for long periods. In summary, therefore, cancer of the breast and of the prostate gland can be made to regress or can be stimulated to renewed or increased growth by hormonal changes in the body. Were we to understand more fully how these changes occur, the desired regressions might be prolonged, occasional instances of stimulation of cancer growth might be avoided, and further insight into the cause and cure of cancer in general might be obtained. Studies of the metabolic pathways of estrogens and androgens in normal and cancerous subjects are needed.

There is a promising field for study of cancer and hormones in the use of estrogens labelled with radio-active isotopes.

STREPTOMYCIN IN THE SURGERY OF PULMONARY TUBERCULOSIS

Murphy says that the Army and Navy have been conducting a co-operative study of the bacteriostatic action of streptomycin on the tubercle bacillus. The surgical divisions of the 47 participating study units were asked to determine whether streptomycin provides any protection against postoperative spread or reactivations and against

the development of empyema in patients subjected to thoracoplasty and pulmonary resection for tuberculosis

The program was initiated in January, 1947. After that date, every alternate patient subjected to thoracoplasty and every patient undergoing lobectomy or pneumonectomy was given streptomycin as a protective agent. It was felt that the use of controls in resection cases could not be justified under present conditions.

In the beginning 2 Gm of streptomycin per day were given by intramuscular injection, divided into five doses. On October 15, 1947, the standard daily dose was reduced to 1 Gm divided into two doses of 0.5 Gm each at 12 hour intervals. It was desired to avoid, as far as possible, the development of resistance to the drug. Under both regimens the drug was administered for one week before and two weeks after each operation. Since the usual interval between thoracoplasty stages was three weeks and the number of stages per patient averaged three, continuous administration of streptomycin for nine weeks has been the rule in the thoracoplasty series.

The results of study concerning the protective action of streptomycin in 1,347 thoracoplasty stages and 129 pulmonary resections for tuberculosis are presented.

The conclusion was reached that streptomycin should not be given to the routine thoracoplasty patient but should be reserved for the occasional borderline risk patient in whom the disease is more widespread and more exudative in character than is usually considered suitable for surgery.

The use of streptomycin is mandatory, however, before as well as after pulmonary resection for tuberculosis.

(Murphy, J. D.) Surgery, Gynecology and Obstetrics 87: 540-558 November 1948. The author is connected with the Department of Surgery, Veterans Administration Hospital, Oteen, N. C.

GARCINOMA OF THE PROSTATE

Arrheim suggests that the bizarre clinical pictures encountered in cases of carcinoma of the prostate are probably the result of the varying and widespread dissemination of metastases. He presents an analysis of the protocols of postmortem examinations of 176 cases in which carcinoma of the prostate was found. The material was drawn from 21,718 postmortem examinations which were performed at Cook County Hospital, Chicago, Ill., during the period from 1929 to 1946, inclusive.

No case was found prior to 42 years of age. There was a great increase in incidence at 60 years of age and 77 percent of the cases occurred between the ages of 60 and 80.

Of the total of 176 patients, 139 died of carcinoma of the prostate and 37 died of other causes. There was the same sudden increase in incidence of carcinoma of the prostate at the age of 60, regardless of whether the patient died of it or whether the carcinoma was an incidental finding.

Ninety-six percent of the carcinomas were adenocarcinomas. Metastases were not discovered in 38 percent of the cases. One-third of all the metastases were visceral. Bone and lymph node involvement constituted 66 percent of all metastases. Perioarticular and tracheobronchial lymph nodes were involved in the order mentioned.

The bladder was most commonly involved by direct extension. Carcinoma of the prostate is biologically active in some patients and inactive in others.

(Aracheli, F. K. Chicago, Ill. *Journal of Urology* 60: 599-603, October 1948. The author is connected with the Departments of Pathology, Cook County Hospital and Northwestern University Medical School, and the Hektoen Institute for Medical Research.)

RESULTS OF THE SYSTEMIC ADMINISTRATION OF THE ANTIBIOTIC, BACITRACIN, IN SURGICAL INFECTIONS

According to Meloney and his associates bacitracin is an antibiotic produced by the Tracey strain of *Bacillus subtilis*. During the past 20 months, purification and standardization have reached a point which has permitted the systematic use of bacitracin. Studies are being carried out with the aid of funds provided by the Medical Research and Development Board of the Surgeon General's Office and the Antibiotics Study Section of the National Institute of Health. The leaders of these groups are co-authors in the presentation of this report.

Bacitracin has a wide antibacterial spectrum, being effective against most strains of hemolytic streptococci, non-hemolytic streptococci, coagulase-positive staphylococci, pneumococci, gonococci, anaerobic cocci in general, all of the gas gangrene group of organisms and the bacillus of tetanus, the diphtheria bacillus and diphtheroids, the spirochetes of syphilis and mouth spirochetes, the actinomycotic group of organisms, and among the protozoans, the *Endamoeba histolytica*. There is little or no action against the large group of aerobic Gram negative non-spore forming bacilli.

The chief advantages that bacitracin has over penicillin are (1) That it is not inhibited by the organisms which produce penicillinase and is, therefore, more likely to be effective in infections due to bacterial mixtures. (2) It is more slowly eliminated from the body and therefore, can be given at longer intervals. (3) Its effectiveness against bacteria is in direct proportion of its concentration. A significant synergistic action between penicillin and bacitracin has been demonstrated in the treatment of experimental syphilis; small fractions of therapeutic doses of each, when combined, yield a therapeutic result. (4) So far, bacitracin has shown less tendency to produce allergic or hypersensitive reactions. Certain strains of bacteria gradually build up a resistance to bacitracin but this is of a low order.

Bacitracin may be used systemically as well as locally in surgical infections. Specifications have been set up by the Food and Drug Administration to safeguard its use in clinical cases.

This report presents the results obtained with the systemic administration of bacitracin in the treatment of 105 cases of surgical infection. For the most part they were cases which had failed to respond to the sulfonamides and to the other antibiotics. There was an overall favorable response in about 70 per cent of these cases and, in about one-fifth of these, the results were dramatic. Of particular interest were three cases of extensive progressive bacterial synergistic gangrene, all of whom responded within 72 hours and recovered without the necessity for surgical excision. In the three largest groups, namely, "cellulitis," "deep abscess" and "infected accidental wound," favorable results were obtained in three-fourths of the cases.

In the dramatic group, the causative organisms were for the most part in the staphylococcal and streptococcal groups. In the latter

classification were found hemolytic, nonhemolytic, microaerophilic and anaerobic streptococci. In a considerable number of staphylococcal strains, the authors found resistance to penicillin and susceptibility to bacitracin.

In 14 percent the results were questionable and in a slightly higher percentage, the results were frankly nil. In most of these cases the causative organisms were resistant to bacitracin.

In the majority of the patients in the whole series there was a transient albuminuria which disappeared either during continued treatment or soon after treatment was discontinued.

Some of the later preparations of bacitracin made by the deep tank method have shown evidence of nephrotoxicity. When the presently available bacitracin is used systemically, there should be repeated tests of kidney function and treatment should be discontinued if there is any indication of serious damage.

(Melencov F L, New York N Y, Altmeier W A, Longacre, A B, Pulski E J and Zintel, H A. *Annals of Surgery* 128: 714-731 October, 1948.)

SURGICAL TREATMENT OF MITRAL STENOSIS VALVULOPLASTY

Harken and his associates point out that the problem of surgery in mitral stenosis is not simply that of breaking down a barrier to the flow of blood through a stenotic orifice. In this report they set forth certain preliminary impressions concerning the selection of patients for operation, the nature of the operation of choice and the surgical handling of the patient.

The authors present the following preliminary classification of patients with mitral stenosis and of the different types in surgery, Group A, patients with low fixed cardiac output—mitral valvuloplasty, Group B, patients with normal cardiac output—artificial interatrial shunt, Group C, patients with uncontrollable tachycardia or with anginal pain—cardiac denervation.

Five operations have been performed. Mitral valvuloplasty was performed in two patients of Group A, with one death. Artificial interatrial defects were produced in two patients of Group B, with survival in each case. Denervation of the heart by bilateral removal of the inferior cervical and dorsal first to fourth ganglions in one patient of Group C was followed by improvement.

These cases are now reported only to indicate the ability of such patients to withstand operation. The evaluation of any long-term benefits attributable to these procedures—and, indeed, of the ultimate position of surgery in mitral stenosis—must rest on objective criteria gained from hemodynamic studies carried out before and after operation. Subjective selection of patients and assessment of results lead to dangerous competitive exercises in surgical techniques rather than to fundamental advances in therapy.

Four principles of the surgery of mitral stenosis have been evolved: the operation should be performed without dislocation of the heart from the position of optimum function, the button-hole opening of the stenotic mitral valve should be approached from the auricular side so that the funnel directs the cutting instrument toward the leaflet margin, surgical enlargement of the stenotic orifice should be so planned that there is a minimum burden from associated regurgitation ("selective

insufficiency") and maximum restoration of valvular function ("valvuloplasty"), and in the presence of mitral obstruction or regurgitation, undue acceleration of the heart rate must be prevented—tachycardia increases pulmonary vascular pressure and is associated with attacks of pulmonary edema and other forms of "pulmonary decompensation"

An unsuccessful attempt at producing "selective insufficiency" is presented. It is suggested that tachycardia was an important factor in the disastrous outcome.

A case report is presented of the survival of a patient with mitral stenosis following an operation designed to produce "selective insufficiency" and "valvuloplasty" of the mitral valve. The authors suggest the need for more extensive and more effective valvuloplastic techniques.

(Harken D. E. Boston Mass. Ellis L. B. Ware P. F. and Norman Leona R. New England Journal of Medicine 239: 801-809 November 1948. The authors are connected with the Eighth Surgical Service and the Surgical Research Laboratory Boston City Hospital and Department of Surgery Tufts College Medical School.)

RESULTS OF RESECTION OF THE VAGUS NERVE FOR CHRONIC PEPTIC ULCER

This study by Miller and Olwin attempts to evaluate results in a series of 101 patients subjected to vagotomy in the past two and a half years, 66 of whom were operated on at the Veterans' Hospital at Hines, Ill., and 35 at the Presbyterian Hospital in Chicago. It involves the work of 18 different surgeons, all members of the American Board of Surgery, and several medical men in these institutions.

For the most part these 101 patients had long-standing chronic peptic ulcer and, for one reason or another, had failed to do well on a medical regimen. In more than half the duration was over 10 years, the longest being 40 years. In 87 the lesion was in the duodenum, in five on the lesser curvature of the stomach and in eight at the stomach after gastroenterostomy or gastric resection. In 47 there was a history of bleeding (often several times repeated), 26 had had perforations, and in 36 obstruction was demonstrable clinically or by roentgenogram. They represented, therefore, situations in which the surgeon was called on to decide between gastroenterostomy, a partial gastrectomy or a resection of the vagus nerves either above or below the diaphragm.

The transthoracic approach was employed in 29 and the abdominal approach in 72 patients.

The postoperative course was in most cases remarkably smooth. The Levine tube was always left in place three or four days. Early ambulation was encouraged. A few patients had a mild pleural effusion and pain in the chest for several days, but in only one instance was it a prominent feature in the months following operation. One woman had trouble swallowing for almost a week, and one had a paralytic ileus, but this passed away in a very short time. Fullness in the abdomen was a common temporary complaint, but diarrhoea was the chief cause of trouble and the most obstinate of all. It was present in 39 patients being temporary in 30, prolonged for several months in two and persistent in seven.

There have been no deaths. Nine patients had left Chicago and could not be traced, which leaves 92 in whom follow-up was possible. In 76 of these the results were good, in 18 they were fair, and in three poor.

The authors conclude that vagus nerve resection, in properly selected cases, has a definite place in the surgical treatment of patients with chronic peptic ulcer who have failed to respond to medical therapy

(Müller E M Chicago Ill and Olwin, J H Archives of Surgery 57 353 360 September 1948
The authors are connected with the Veterans Hospital Illinois Ill and the Presbyterian Hospital Chicago)

Book Reviews and Notices

A TEXT BOOK OF BACTERIOLOGY by N G Pandalai M D, D T M, F R C P, (Edin.), pp viii 748, 22 x 15 cm The Bangalore Printing and Publishing Co, Ltd, Mysore Road BANGALORE CITY 1948 Price Rs 18/-

There are few successful text-books written by Indian teachers for their students. Writing a text-book, if it does nothing, at least, teaches the writer, it also puts him where he belongs. We welcome this text-book of Bacteriology by Prof Pandalai, which in many respects fulfils the requirements of a suitable handbook for undergraduates. The arrangement of the subject matter is along the traditional lines into general and special or systemic bacteriology. It is gratifying to find that an attempt has been made to bring every chapter up-to-date. A few omissions have inevitably crept in. For instance, under the laboratory diagnosis of small-pox, no mention is made of the simple technique of Paschen's smear method. Despite the disarming apology in the preface, the exclusion of a chapter on the history of bacteriology is inexcusable. Historical aspects have their inherent interest. A simple story of the principal advances and their sequential development is forever a stimulating exercise, and for the proper appreciation of contemporary knowledge, it is necessary to have some acquaintance with its historical background. Perhaps in the next edition it would be well to condense the chapter on the microscope (it runs into nineteen pages) and utilise the pages so freed to amend the above omission. It will also be worth bearing in mind that tables of the statistical data are far more effective in impressing the efficacy of the prophylactic and curative measures in infectious diseases than wordy statements. On the whole the book is easily read but at many places the style becomes laborious and clumsy. For a book which contains only twelve illustrations (another serious defect) the price is rather high. These small defects could be easily remedied in the next edition. We wish Dr Pandalai's text-book a successful career.

N M P

Notes on New Drugs

NEOMYCIN

Waksman has reported the discovery of a new antibiotic, *neomycin*, produced by a different species of streptomycetes, than the one which produces streptomycin which was also discovered by Waksman in 1944. Experimental work on neomycin suggests that neomycin is as active against streptomycin-resistant strains of tubercle bacilli as against the streptomycin sensitive strains, is active *in vivo*, is less toxic than streptomycin, and upto the present has not induced bacterial resistance. It is basic, heat-stable and soluble in water. The drug is still in the experimental stage and not available for clinical use.

P.A.S. (AMINACYL)

Sodium Salt of p-aminosalicylic acid in form of dragees for chemotherapy of tuberculosis by mouth

The pronounced bacteriostatic effect of p-aminosalicylic acid (PAS) with regard to the tubercle bacillus manifests itself both in cultures and in animal experiments. *In vitro*, PAS inhibits growth of pathogenic tubercle bacilli at dilutions as high as 1:10,000,000 to 1:650,000. Thus, its activity closely approaches that of streptomycin. Experimental tuberculosis in mice may be best controlled with daily doses of 0.3–0.6 gm per kgm body weight.

Corresponding doses of AMINACYL WANDER also modify in an impressive manner the course of tuberculosis in man especially the toxic exudative forms, temperature usually drops to normal within a few days, the patients put on weight and their general condition improves. Simultaneously, the blood sedimentation rate usually decreases, the amount of sputum and the number of bacilli in the expectoration diminish. Certain authors have seen evident signs of morphological degeneration of Koch's bacillus. As the fever drops, there are no accesses of perspiration and, in general, neither therapeutic nor even toxic doses of PAS show any salicylate effect.

In order to obtain such clinical results, past experience shows that daily doses of 10 to 15 gm with an average of approx. 12 gm of the free p-aminosalicylic acid are usually necessary. While the free acid given in such quantities frequently leads to irritation of the gastro intestinal tract, the required doses are easily taken by the patient and are well tolerated in the form of dragees of AMINACYL WANDER containing the sodium salt of PAS.

These relatively high doses, compared with other drugs, are required because of the very rapid elimination of PAS through the kidneys. On the other hand, such a dosage is possible due to the extremely low toxicity of PAS, which, in the animal experiment for instance, is 3–4 times lower than that of sodium salicylate.

In order to maintain an effective blood level of 3 to 8 mgm %, it is usually necessary to administer 4 times daily 3–4 gm of the sodium salt (10 dragees each time) at regular intervals, although no diminution of the effect is caused by allowing the patient to sleep the whole night through. Likewise, it has proved possible to limit the medication to 4 or 5 days each week, with intermediary rest periods of 2 or 3 days. At the start of treatment, temperature has a tendency to rise slightly during such rest periods, but later on it stays normal.

Although clinical trials were begun in 1946, nothing definite can be said as yet concerning dosage and mode of application. An average dose of 12 gm daily seems unavoidable, however it will certainly be possible to vary considerably the mode of administration by means of shorter or longer intervals between periods of medication. At any rate, the individual doses should never be scattered indiscriminately if sufficiently high blood levels are to be obtained.

The question of a possible PAS resistance of the tubercle bacillus remains to be answered. However, experimental results seem to indicate that the bacillary sensitivity increases rather than decreases during treatment. Furthermore, streptomycin resistant cases react just as favourably to AMINACYL medication as streptomycin sensitive ones.

Careful studies of any possible toxic effects, particularly with regard to the blood, have given only negative results. Likewise, renal function does not seem to be adversely affected in any way by AMINACYL.

The remarkable diffusion of AMINACYL given by mouth permits the drug to reach almost all organs. Thus the same concentrations have been found in pleural exudates as in the blood, and in the cerebro spinal fluid 40 to 60% of these concentrations.

According to clinical experience, several forms of extrapulmonary tuberculosis seem to react in a singular manner to PAS treatment. Several authors report that in cases of renal tuberculosis they have seen the bacilli disappear in a very short time from the urine; likewise, abdominal tuberculosis is said to react just as favourably with reference to general symptoms as lung tuberculosis. A wide field of therapeutic possibilities opens up for the local treatment of tuberculous infections with AMINACYL, especially for pleural empyemas, fistulae, abscesses, etc., more detailed information concerning this mode of application may be found in the circulars for AMINACYL-ampoules for local treatment.

(AMINACYL WANDER dragees contain 0.34 gm each of the sodium salt of p-aminosalicylic acid corresponding to 0.3 gm of the free acid.)

AMINACYL WANDER dragees are sold in packages containing 250 and 1000 dragees.)

HETRAZAN

Elephantiasis, which for centuries has been the scourge of millions in tropical lands around the world, especially in the Far East, may be stamped out if early success of this latest drug proves permanent

"Hetrazan," developed by Lederle Laboratories of New York, has been tested extensively in British Guiana and the Caribbean Islands and notable results reported. Fourteen thousand inhabitants of Saint John, in the Virgin Islands, have been treated, and when scientists return to this island later this year, they will know definitely whether the effects are permanent or not.

The initial success of Hetrazan on oncofilaria, a similar disease prevalent in Mexico and Guatemala, also has been reported by Lederle.

However, the most dramatic hope is held out for the sufferers of filariasis. Lederle scientists do not claim Hetrazan will cure elephantiasis, although a slight reduction of the grotesque swellings which occur have been reported. However, they do claim the drug will neutralize carriers, and thereby stop the spread of the disease and eventually cause its elimination.

Filariasis, commonly known as "big foot," is caused by adult worms living in the human lymphatic system. Each worm regularly produces thousands of embryos called microfilariae, which circulate in the blood of the infected person. Like malaria, the infection is transmitted by mosquitoes, which deposit microfilariae in the skin. Tiny germs develop into adult worms which, in turn, produce their embryos, and the whole cycle begins anew.

Hetrazan, Lederle scientists claim, breaks the cycle by ridding the blood stream of microfilariae, thus making it impossible for mosquitoes to infect healthy persons.

PALUDRINE

It is recommended that Paludrine may be used in the following dosages:

(1) *For protection against malignant tertian and suppression of benign tertian malaria*—0.3 Gm. once weekly, or 0.1 Gm. twice a week at 3 and 4-day intervals.

(2) *For radical cure of malignant tertian malaria*—0.3 Gm. twice daily for 10 days.

(3) *In benign tertian malaria*, the greatest hope of a radical cure with Paludrine is offered by the dosage regime of 0.3 Gm. daily until the fever subsides, and then 0.3 Gm. once a week or 0.1 Gm. twice weekly at three and four day intervals for about 6 months.

(4) For "clinical" cure of all types of malaria—0.3 Gm. daily until the fever subsides.

(5) For children over ten, the dosage for adults is indicated both for treatment and prophylaxis. Children under ten should be dosed according to age and size, but the minimum given to any child, however young, need not be less than 0.025 Gm.

Paludrine is now made available in these two new sized tablets of 0.3 g. and 0.025 g., besides the usual size of 0.1 g. tablets.

The Indian Physician

VOL VIII NO 8

AUGUST 1949

WHOLE NO 92

Original Contributions

STERILITY PROBLEM AS IT AFFECTS THE FEMALE*

by

Dr B N PURANDARE,

M.D., F.C.P.S. (Bom), F.R.C.S. (Edin), F.I.C.S.
K. E. M. Hospital, BOMBAY

The problem of sterility from a gynaecological point of view is such an important one that it won't be an exaggeration to state that more than two third of the gynaecological practice is one way or the other, directed to overcome the problem of infertility. But it would be impossible to do justice to all the aspects of this problem in the short time assigned to my paper and I will, therefore, restrict myself to certain aspects only realising fully well that the factors like pH of the vagina, the penetrability of the cervical mucous plug, the enzymic action of hyaluronidase, basal temperature, ovarian and pituitary hormones in the blood and urine and the B. M. R. studies etc are equally important. The investigation of a sterility case can not be considered complete and thorough until all or most of these investigations are carried out.

The male is supposed to be responsible for one third of the cases of sterility. In the gynaecological out patient department, every patient who comes for the treatment of sterility, has her husband investigated from the point of view of the sperms. During the last six months the seminal fluid examinations were carried out in 225 husbands and out of them 25 were found to have azoospermia, i.e., the incidence being 11%. In these azoospermic husbands repeated examinations were carried out as far as possible with the usual precautions and six cases definitely showed consistently the same results in the subsequent repeated examinations on 4-5 occasions. Unfortunately it is difficult to investigate these husbands in general hospital as most of them never come back with their wives for any further examination and treatment once they come to know that they are responsible for the sterility. The detailed discussion has already been undertaken by the previous speaker and the statistical aspect of the seminal fluid is presented here for the sake of comparison.

Another aspect of the seminal fluid which is at present receiving a good deal of investigation is the estimation of hyaluronidase in the seminal fluid. This enzyme is supposed to dissolve the corona radiata cells surrounding the ovum, thereby facilitate fertilization. Some investigators have obtained very good results by depositing a small

* A paper read at the 91st meeting of the G. S. Medical College and K. E. M. Hospital Staff Society, held on Saturday, the 9th April 1949.

quantity of this enzyme in the cervical canal instead of artificial insemination. The results have been equally encouraging. In non-obstructive type of azoospermia the husband is advised to take a nourishing diet rich in protein, vitamin B complex and vitamin E by mouth, and thyroid extract in properly graduated doses. He is also advised to take a follicular maturing hormone injections and not the testicular hormone for the latter may depress the function of the pituitary and may favour further azoospermia.

TABLE A

Total number of males investigated	225
Sperms present in	200
No sperms in	25—11%
Absolute azoospermia by repeated examinations	6

In the female the problem of sterility had to be investigated from three aspects (1) Ovogenesis, (2) Patency of the genital canal (3) Quantity, quality and pH of the genital secretions.

The ovogenesis is confirmed directly by Culdoscopic examination of the surface of the ovary and indirectly by noting the basal temperature variations, hormone estimations in the blood and urine, particularly detection of Pregnanediol glucuronide and by detecting a secretory phase in the endometrium secured by suction biopsy. I intend to give the results of these histological examinations as carried out from the out-patient department of our hospital. In 108 females endometrial suction curettage was done in the out door by Novak's Suction Biopsy Curette and 50% of the patients showed a secretory endometrium. The rest of them had the endometrium in the proliferative phase in spite of the fact that the endometrium was removed just before the menstrual period was expected. But these negative results have no confirmatory value unless the test is repeated in three to four successive cycles. In two cases early pregnancy with decidual reaction and presence of chorionic villi was reported even though the biopsy was carried out in these sterile women a few days before the expected period. T B of the endometrium was noted in 8% of the cases.

TABLE B
DIAGNOSTIC CURETTAGE

(From 8-9-1948 to 31-3-1949)

Total number of diagnostic curettage	103
Proliferative phase	50
Secretory phase	48
Pregnancy with decidua and chorionic villi	2
T B Endometritis	3

The occurrence of ovulation can be further confirmed by the basal temperature chart recordings and the exact time being detected for carrying out the artificial insemination and for advising the patient the most probable time for successful coitus. I have seen the benefits of these procedures in good many private cases. If there is a failure of ovulation, patient requires heavy doses of follicular maturing and luteinizing hormones by parenteral route and thyroid extract and vitamin B & C by mouth. In one of my patients pregnancy followed in spite of an ovulatory cycle and one child sterility of 18 years and the patient is now

advanced over 8 months in pregnancy I have never ventured yet to favour ovulation by giving stimulating doses of deep x-ray to the pituitary and ovary

TABLE 1

Type of Curve	Primary Sterility		Secondary Sterility	
	With Anaesthesia	Without Anaesthesia	With Anaesthesia	Without Anaesthesia
	No of cases & %	No of cases & %	No of cases & %	No of cases & %
	125	188	40	150
Normal	80 (64 0%)	81 (44 3%)	29 (72 5%)	76 (50 7%)
Low	11 (8 8%)	27 (14 7%)	5 (12 5%)	18 (8 7%)
High	2 (1 6%)	6 (3 3%)	1 (2 5%)	2 (1 3%)
Spasm	14 (11 2%)	16 (8 7%)	2 (5 0%)	5 (8 8%)
Platau	7 (5 6%)	19 (10 4%)	3 (7 5%)	27 (18 0%)
Blocked	11 (8 8%)	34 (18 6%)	NIL	27 (18 0%)

The patency of the genital canal was investigated by kymographic tracings. These give much more information than the old auscultation method. The height of the curve and the character of the tracings not only indicate the mechanical aspect like the patency of the tubes, but also it supplies the information regarding the physiological function of the uterus and the tubes, their motility and the tone and oestrin production in the body. The recorded curves can be grouped under the following varieties—(a) Normal curve, (b) Low curve (c) High Curve, (d) Spasm curve, (e) Platau curve indicating a gradual leak and a partial block, (f) Complete block curve. Four hundred and ninety-eight cases were investigated for tubal patency. For the sake of comparison and for deducing conclusive findings the cases were grouped into primary sterility and secondary sterility and with and without anaesthesia. The results are given in the tables 1, 2 and 3.

TABLE 2

RESULTS	Primary Sterility		Secondary Sterility	
	With Anaesthesia	Without Anaesthesia	With Anaesthesia	Without Anaesthesia
	No of cases & %	No of cases & %	No of cases & %	No of cases & %
Tubes Patent	114 (91 2%)	149 (81 4%)	40 (100%)	128 (82 0%)
Normal patency	93 (74 4%)	114 (62 3%)	35 (87 5%)	91 (60 7%)
Spasm	14 (11 2%)	16 (8 7%)	2 (5 0%)	5 (8 8%)
Partial block with gradual leak	7 (5 6%)	19 (10 4%)	3 (7 5%)	27 (18 0%)
Tubes Blocked	11 (8 8%)	34 (18 6%)	NIL	27 (18 0%)

1 The conclusions from these tables can be briefly stated as follows - Blocked tubes should be expected in 18% of the cases when the test is carried out without anaesthesia, but under anaesthesia the incidence may be as low as 8%. The anaesthesia used in these cases was Sodium Pentothal intravenously and 100 mg of Demerol as a basal narcotic.

2 At subsequent kymographic tests in patients with tubal block 50% of the primary sterility cases and 16% of the secondary sterility group cases, tubes were seen to be patent. This may be either due to the effect of medical treatment during the intervening period or due to the less prominent nervous factor in the subsequent tests.

3 The results of medicinal treatment are much more encouraging in partial obstruction and gradual leak cases which showed a normal curve at subsequent examinations in over 60% of the cases both in the primary and secondary sterility groups. Hence no definite prognosis should be given in blocked tubes cases and any major abdominal operation like Salpingostomy be undertaken unless repeatedly confirmed by subsequent examinations or by carrying out a hysterosalpingographic study of the patient so as to confirm the diagnosis and determine the exact site and nature of obstruction. The patients with gradual leak or total obstruction were given a course of milk injections, vaginal diathermy and vaginal douching. Iodides and oestrin preparations along with Vitamin B and Folic Acid and Thyroid Extract were also administered during the intervening period.

TABLE 3
Results at the subsequent tests

Type of Curve	Primary Sterility	Secondary Sterility
Blocked Tubes—total cases	10	6
Blocked tubes opened	5	1
Blocked as before	5	5
Gradual leak—total cases	11	5
Gradual leak opened	7	3
Gradual leak as before	4	2
Normal patency—total cases	20	12
Normal as before	20	12
Normal—subsequently blocked	NIL	NIL

The results of salpingostomy operations are so unsatisfactory that every year new methods are suggested to improve the end results. Successful results are noted in 3 to 9% of the cases of Salpingostomy depending upon the type of operation and degree of the quiescence of infection. In this respect side Salpingostomy is least successful. Bonneys Cuff Salpingostomy appears to be more helpful in keeping the end of the tube patent. Recently a trap-door salpingostomy has been described by H. W. Johnston of University of Toronto and in 3 of his cases patient became pregnant within a year. A preliminary insufflation of air just before opening the abdomen determines the patency of the uterine end of the tube by the presence of air bubbles in the hydrosalpinx as it is opened. Lately I have used this procedure. During the course of last 9 years I had to carry out salpingostomy on twenty occasions in my private patients and nearly half a dozen times in K. E. M. Hospital. The type of salpingostomy done was as far as possible Cuff method unless it was anatomically or technically not possible when lateral or end salpingostomy was carried out. For the last couple of years I have been carrying out the blowing out of the tube within a week after the operation and the number of successful salpingostomy is increased. Table 4 gives the details of the operative procedure.

TABLE 4

Salpingostomy—20 cases	Primary Sterility 6 cases	Secondary Sterility 14 cases
Cuff Salpingostomy	6	11
Bilateral Cuff Salpingostomy	2	1
End Salpingostomy	1	2
Lateral Salpingostomy	1	1
Salpingolysis	2	6
Salpingectomy on the other side	0	5

Our present Antibiotics and Sulfa drugs will certainly help to enhance the success of the plastic surgery on the tubes and few years of clinical experimentation alone will decide the success achieved by and progress made in the tubal surgery

REFERENCE

1. JOHNSON H. W. The 1948 Year Book of Obstetrics and Gynaecology pp 338, Chicago The Year Book Publishers, 1949

STERILITY IN THE MALES

by

Dr G M PHADKE, FRCS (Eng)

K E M Hospital Parel, BOMBAY

For many centuries until the present, the wife has borne the burden of blame for failure to produce off-spring. This indifference to the male was due to prejudices and misconceptions. The medical profession also was not entirely free from this outlook. In 1868, Dr Sims, addressing the medical society on the use of microscope as an aid in the diagnosis and treatment of sterility, advocated the importance of demonstrating spermatozoa in the semen. He complained that he "was misrepresented, maligned and positively abused both in America and abroad," for his insistence of semen studies cited the *Medical Times and Gazette*, which charged most "This dabbling in the vagina with speculum and syringe was incompatible with decency and self-respect." Nearly half a century had passed before the medical men began to accept his teachings as ethical and desirable.

The erroneous belief that patency in the male was ample evidence of fertility is no longer tenable. Besides the fear of offending the masculine ego by doubting his ability and the danger of discovering a previous venereal disease were responsible for preventing any scientific studies in the male.

Fertility is a divided responsibility shared equally by the husband and the wife. From the beginning of this century only, serious attention has been given to the male in fertility. According to Hotchkiss, the husband is responsible for nearly 25% of sterile marriages. The man's share therefore is not so rare as was thought once upon a time.

After marriage, one year of involuntary sterility justifies the carrying out of a complete diagnostic study. A year or two in young couples would not make much difference but when the woman is 30 years old, no time should be lost. From 30 years onwards there is a steady diminution in the peak of fertility, so that delay in investigations may lessen chances of a successful result.

Sterility in the male is a complex problem requiring urologic, endocrinologic and laboratory studies. Roughly all cases can be classified into two main groups —

- 1 Urologic, and
- 2 Endocrinologic

The urologic group can be subdivided into congenital and acquired. The former includes cases of hypospadias, cryptorchidism and cases with abnormal attachments of epididymis to the testis. The acquired group includes cases due to infections of the genito-urinary tract by specific or non-specific organisms.

Clinical Examination of the Male — Particular attention is paid to the general appearance, distribution of fat, height, blood pressure and secondary sexual characteristics. The external genitals are examined for any abnormalities. For proper conception the semen should be deposited in the vicinity of the cervix. This is not possible in the case of penile hypospadias and partly so in the glandular variety. Testicles may be smaller in size and softer in consistency. Normal size and consistency of the testicles are of no assurance however that healthy spermatozoa are being produced in it. Epididymis and vas are examined for any abnormality. If prostate, seminal vesicles and urethra are pathologically affected, proper treatment is directed towards them. Semen is examined next. The details of this examination are already given by Dr Vaidya. Appraisal of the semen constitutes the chief and the final index of fertility in the men. Our interest is aroused if the semen does not contain any spermatozoa. Aspermia may be due to either atrophy of the testicles or obstruction to the passage between the ejaculatory ducts and the globus major.

The diagnosis of obstruction of the ejaculatory ducts is found out by failure to obtain any contents from the seminal vesicles after massage and also by an urethroscopic examination. The dilatation of the ducts through the urethroscope does not usually succeed.

The testicular puncture or testicular biopsy are the methods by which we can decide whether spermatogenesis is present or not. Huhner advocated testicular aspiration in 1913. Technique of this is the same as in aspiration biopsy under local anesthesia. The material obtained is unfortunately very little, and there is a chance that the active seminiferous tubule may not be punctured. Again lesser faults of spermatogenesis leading to varying degrees of oligospermia may not be diagnosed. The method is only reliable if spermatozoa are seen. We have done this on eight patients. In only one of them we were able to see an occasional spermatozoa under the microscope after a prolonged search. We discarded this method in preference to testicular biopsy, a method more reliable to decide the state of testicular function. This was performed experimentally by Engle and was first used clinically by Hotchkiss of New York.

Technique —Ten c.c. of 1% procaine is injected into the cord. Next the testis is grasped and the anterior surface is presented. The skin of the scrotum is held taut and local injections are given. An incision 1.5 cms. long is made in the skin of the scrotum and this is deepened until the parietal layer of tunica vaginalis is opened which is recognised by an escape of a little fluid from the sac and the pearly white appearance of the tunica albuginea. Small retractors as used in the ophthalmic department will expose the anterior surface of the testicle. A tiny incision is made through the tunica albuginea. There is usually a brisk haemorrhage at this stage, but it always stops after stitching the gap. Once the tunica is cut the seminiferous tubules pout out into the wound. If not they can be teased out with a blunt probe. The exposed portion of the tubules is snipped off with a tiny pair of scissors and preserved in Bovin's fluid for sectioning. Incision in the tunica is closed with a very fine linen or silk thread. Skin of the scrotum is stitched in the usual way. Other side is tackled in the same manner, and a supporting bandage is given. It is not necessary to hospitalize the patient. But majority of them do get some discomfort for the next two days and this prevents them from attending to their work. The section will conclusively show the abnormality of the seminiferous tubules and whether spermatogenesis is taking place within them or not. If gross dysfunction is detected, further time and money of the patient is saved. We have carried out this test on eleven patients, in eight of them spermatogenesis was good and very poor in three. If the biopsy study is positive, and no spermatozoa in the semen, the only conclusion is that there is some obstruction between the tests and the lower end of the vas. This can only be discovered by an open operation.

Technique —This operation should be done six weeks after the testicular biopsy. Under local anaesthesia, the testicle, epididymis and the scrotal portion of the vas are brought out through an adequate incision through the scrotal skin. Tunica vaginalis is opened and epididymis is examined, an oval window is made in the globus major and some milky fluid will be seen coming out. This is aspirated and put on a slide, for microscopic examination in the theatre for the presence of spermatozoa. If not found further operative procedure is not necessary as it shows that the obstruction is between the epididymis and the testis. The results of the operation where vas is joined to the testis are disappointing as all of them ended in failures. Fortunately in the majority of cases the obstruction is in the region of the globus minor, so an operation of vaso-epididymostomy is possible.

Next step is to decide about the patency of the vas. A portion of the vas near the globus major is selected and separated from the surrounding structures for an inch or two. Complete stripping of the vas should not be done as its blood supply would be interfered with. By holding it between the thumb and the forefinger of the left hand an oblique cut is made through its anterior half. The gap is opened and a silkworm gut thread is passed into its lumen, distally as far as it can go. If no obstruction is present it can be very easily passed. This procedure however will not conclusively prove the patency of the pelvic portion nor will it show that the ejaculatory ducts are patent. But obstruction at these sites cannot be corrected by any operative procedures so far at our disposal. Again it has been found that the at v es

obstructions are very rarely met with. So if a fair length of the vas is patent, operation of vaso-epididymostomy is carried out. Another method to detect the patency of the vas is to inject some coloured solution into the lumen, and to recover it from the urine in the bladder. The coloured material, mercurochrome, methylene blue or argyrol, stain the tissues in the operative field and identification of structures is difficult. We have not used this method as a routine.

Earlier failures of vaso-epididymostomy were due to the material used for suturing. Catgut should not be used as it produces fair amount of tissue reaction and occludes the tiny lumen of the vas. Hanger used very thin silver wire, in his successful cases. But the thin wire is not very easy to handle. Hotchkiss, after some experimental work used arterial silk successfully. We have used this material and his technique of union in all our cases.

Having ascertained the patency of the vas a blunt hypodermic needle is passed into its lumen for a distance of 1.5 cms. The anterior wall of the vas is cut open. This opened out portion of the vas is united to the oval window made in the epididymis by two stitches at the upper and lower end and a stitch or two at the sides. To minimise the tension at the site of union, additional supporting stitches are taken in the tissues in the neighbourhood. Testis and epididymis are put back into the scrotum and the incision is closed. The same procedure is carried out on the other side.

The operation is tedious but not harmful to life. Some surgeons prefer to do it under general anaesthesia. I have done all these operations under local. Patient is hospitalised for five to six days and is discharged after the removal of stitches and is asked to use scrotal support.

Semen should be examined every three months after the operation until spermatozoa are seen, which may take as long as one year to appear. Another attempt may be made after one year if desirable.

We have carried out the above procedure on five patients after a regular testicular biopsy.

CASE REPORTS

Case No 1 —As vas was severely blocked in the lower scrotal part inguinal portion was anastomosed to the globus major and thus resulted into failure probably due to tension on the suture line.

Case No 2 —Not traceable.

Case No 3 —Operation was performed after seventeen years of married life. Though semen was negative, testicular biopsy showed sperms. 4 months after operation sperm count of semen was 56 millions/cc. At present, the patient's wife has got three months pregnancy.

Case No 4 —After having children from his first wife, vasectomy was done 10 years ago. As he remarried 6 years ago, and as semen was negative for sperms vaso-epididymostomy was done and 3 months after, few spermatozoa were seen in the semen. No further follow up.

Case No 5 —A patient, an old case of gonorrhoea, married six years ago, had no sperms in semen but as testicular biopsy was showing sperms, vaso-epididymostomy was done at the K. E. M. Hospital 2 months ago, and upto now semen does not contain spermatozoa.

SEMINAL FLUID IN CASES OF STERILITY

by
Dr K N VAIDYA, M D (Bom)
K E M Hospital BOMBAY

To procreate is an instinct with every living being and man is no exception to it. Cures for sterility are a legend and in every country people who cannot beget have ransacked everything from the temple to the chemist's shop for a cure. In China wherever you see a statue of Kwan Yin, the goddess of childbirth and fertility, you always find that the kneeling stone before it has been worn inches deep by the knees of supplicants. We in this country are familiar with all sorts of Mantartantras being tried as a cure for sterility. Uptil recently it was taken for granted that the fault in a childless marriage lay with the female partner. The outlook has now changed and it has been found that quite often the fault lies with the male. Examination of semen has changed this outlook.

The present paper is an analysis of fifty cases where the semen was examined. All excepting two were referred by practitioners for childless marriage. Of the remaining two one was a bachelor and wanted to know whether he was potent and the other came because his wife used to get a burning sensation in the vagina after the discharge of the semen.

Collection of the material —Collection of the material is an important factor and due care must be taken to collect the sample. Before collecting the sample the patient should be asked to refrain from an intercourse for four to five days. For collection of the semen there are three methods (1) By masturbation, (2) By coitus interruptus and (3) by intercourse using a condom. I have preferred the first method because in that case one can get the sample for examination almost immediately. No special arrangements are necessary and there is no difficulty about transport. Most patients prefer this method. Sometimes patients find it impossible to get the semen by this method. In that case I had advised the second method namely coitus interruptus. The patient was supplied with a wide mouthed bottle and was asked to bring the semen as early as possible to my rooms. The third method is not advisable because very often the condom contains chemicals which are injurious to the sperms and sometimes such a lot of powder is present in the condom that it interferes with the examination. I have rarely advised this method. Should it be necessary to use this method it is advisable to instruct the patient to wash the sheath thoroughly and dry it before use.

As soon as the sample is received in the laboratory the sample should be examined. I have carried out the examination under the following heads (1) Volume (2) Viscosity (3) Sperm Count (4) Motility of sperms immediately after the sample is received and motility at the end of 6 to 8 hours (5) Presence of abnormal sperms (6) Presence of pus cells and (7) Presence of organisms. I will now deal with each one of these heads individually.

A paper read at the 91st meeting of the Seth G.S. Medical College Staff Society held on Saturday, the 9th April 1949

Volume.—The volume of the semen varies from case to case. In my series it has varied from 0.6 c.c. to 6.0 c.c. The average volume is from 2 to 4 c.c. The volume is no criterion of fertility unless it is very small. In my series the semen which had a volume of 6 c.c. had a very poor sperm count and whatever few sperms were present were completely non-motile.

Viscosity.—The semen as soon as it is passed is quite viscous but liquifies at room temperature in about 15 to 30 minutes. Some specimens are known to remain viscous for a long time and it is claimed that increased viscosity reduces the chances of spermatozoa reaching the cervical canal. In one of my cases the viscosity was increased and even after keeping the sample for twelve hours the sample did not liquify to any appreciable extent. A wet film examination showed that the sperms had great difficulty in making movements because of the increased viscosity. Another disadvantage of increased viscosity is that the sperms have to utilise their energy to move through the viscid medium and it is quite likely that their longevity is reduced.

Motility of the sperms.—It is now a well known fact that sperms have to travel the whole of the female genital tract to impregnate the ovum. To do this not only must the sperm be actively motile immediately after discharge but the motility should be a sustained one for a few hours. For studying the motility of sperms an ordinary wet film examination is sufficient. It should be noted that the initial motility of the sperms in a freshly ejaculated semen is rather poor. When liquifaction has taken place (which as has already been stated takes from 15 to 30 minutes) the motility becomes marked. The motility should be studied from three points of view: (1) percentage of active cells, (2) type of motility and (3) duration of motility. In a good specimen about 80 to 95% of the sperms should be actively motile when freshly examined. Such a specimen exhibits little cessation of activity at the end of third hour and considerable cellular activity is present at the fifth or sixth hour. A few sperms are still active when the specimen is examined at the end of twenty-four hours. The types of motility could be described from excellent or aggressive to absolutely no motility. In my series I have studied the motility in the fresh specimen and then after every three hours upto a total duration of 8 to 10 hours. I will deal with my figures regarding the motility of sperms when I am dealing with the sperm count.

Sperm count.—The total count of sperms taken together with the motility of sperms forms the most important part of the examination of the semen. There are no absolute figures regarding the normal human sperm count and different authors give different figures. Meaker for example states that most highly fertile men have counts of over 100 million per c.c. and in his experience no pregnancy has occurred where the count was below 60 million per c.c. Macomber and Saunders, however, report that in 244 cases of sterile and fertile matings they had four fertile couples with counts of less than 60 million and it is said by some authors that everything else being normal counts as low as 10 million per c.c. are sufficient to ensure fertilisation. In giving my reports I have treated figures above 70 million as normal, between 10 and 70 million as moderate and figures below 10 million as poor specimens.

The total count of sperms is a simple procedure. I either use the red cells or the white cells pipette, depending upon a rough estimate of the total count as seen by the wet film examination. The diluting fluid that I use now-a-days is physiological saline to which has been added carbol fuchsin in the proportion of 0.1 c.c. to 100 c.c. Formerly I was using a saturated solution of sodium bicarbonate. Both diluting fluids work quite satisfactorily. Semen is taken up to 0.5 or 1 mark and diluted with the diluting fluid. I have done all my counts on Neubauer's chamber counting all the sperms in the ruled area. The calculation of course varies according to the dilution used. The number of sperms are expressed as so many per c.c.

As already stated I have examined the semen of 50 cases. A total of 56 samples was examined from these cases. In four patients a sample was examined twice and in one case thrice. These fifty cases could be classified as follows taking the sperm count and their motility into account:

(1) 14 patients had aspermia, that is not a single sperm present in the whole sample.

(2) 16 patients had a count less than 10 million per c.c. In 4 of them the motility was good, in 7 fair and in 7 bad.

(3) 16 patients had a count varying between 10 and 70 million. In 10 the motility was good, in 3 fair and in 3 bad.

(4) 4 patients had a count of more than 70 million per c.c. and out of these one case is of a bachelor about whom I have already mentioned in the earlier part of my paper. The motility in this group was excellent in all cases.

One thing stands out prominently when one looks at these figures and it is the number of cases that have got complete Aspermia. They are as many as 14. Adding to this group those cases with a count of less than 10 million (a figure which I have arbitrarily chosen as one below which fertility is extremely difficult if not impossible) it will be seen that there are thirty cases out of 48 sterility patients where the defect lay with the man. That calculates to a percentage of 62.5%, a fairly big percentage. I might mention that in those cases which I have labelled as aspermia I have made repeated wet film examinations from those specimens and ultimately centrifuged the material to see if any sperms are present. These cases were labelled as aspermia only when no sperms were present as seen by these methods. It is argued and I think correctly by many authors that examination of a single specimen should not be taken as a conclusive evidence regarding the absence of sperms and repeated examinations should be done before a diagnosis of aspermia is pronounced, but in private practice it is extremely difficult to get the same patient submit to the semen examination more than once. Hence I had to remain satisfied with a single examination. Even when a diagnosis of aspermia has been made and no hope exists such a verdict should not be given to the patient while talking to him, because we are not quite sure whether the aspermia is a permanent feature with that patient.

This much is for the general observations on the count of sperms in the semen examination. I will now quote few cases from the record. These are cases where I had the opportunity of examining semen more than once. There are four such cases in my series,

Case No 1 The patient had aspermia on both occasions the semen having been examined with an interval of one month during which he had taken a course of injections

Case No 2—The patient had a count of 35 million per c c with no motility of sperms. He took a course of injections and the semen was examined three months later and this time the count was 46 millions per c c and a few of the sperms were motile though the motility ceased within four hours. This patient did have a child after one year.

Case No 3—This patient's counts were done thrice. In between he had taken a number of injections. The count on the first occasion on 4-8-1942 was 2 million with no motility. On 27-8-1942 it was 11 million with no motility. It was last done on 8-2-1949 and was 16 million with a fairly good motility. He has no child uptil now though his wife has undergone the usual gynaecological treatments.

Case No 4—This was a patient who gave a definite history of gonorrhoea. His semen was examined at the interval of five months. No sperms have been present on both occasions but instead a large number of pus cells were present. The semen was as a matter of fact nothing else but pus. Gram's stain of the smear showed a large number of Gram negative bacilli but no gonococci.

Morphology of the sperms—A good deal of attention has latterly been given to the morphology of sperms. Abnormal morphology is supposed to prevent conception. Moench is an advocate of this theory. He places great weight on the structure and the shape of the head of the sperm and believes it to be of far more importance than the other items discussed in the semen analysis. Other authors disagree with this hypothesis and believe that the accurate estimation of fertilising ability depends on a combination of factors namely the volume, the number of sperms, their motility and their endurance and not on any one alone. Even in a normal semen some abnormal sperms are found and about 10 to 15% abnormal sperms are not given much significance. In my series of cases I have not examined the morphology in the first few cases. I have been doing it latterly and in one case I have found as many as 28% abnormal forms. This was the same specimen in which the viscosity of the semen was also markedly increased. I have been studying the morphology by making an ordinary smear and staining by Gram's method. This is not an ideal method for studying the morphology of sperms. Hotchkiss and Eastman have advocated fixing the smear in Schaudin's fluid. The smear is then successively treated by 50% alcohol, eosin, acid alcohol and hematoxylin. I have not used this method.

Pus cells—The presence of a few pus cells (about 4 to 6 per high power field) is quite common in seminal fluid and has no pathological significance. Presence of large number of pus cells of course means that some infection is present. In my series as I have already said that there was one case of old gonorrhoea and the semen was nothing else but pus.

Organisms—Normally no organisms are found but in infected cases the causative organism may be found. In my series in the same case which I have mentioned above a large number of Gram negative bacilli were found on two successive occasions. I have not encountered any case which showed the presence of gonococci.

SUMMARY

- (1) An analysis of 56 samples of semen has been presented
- (2) In a large number of cases of barren marriages the fault lies with the male partner and it is revealed by examination of semen.

(3) In evaluating semen its volume, viscosity, total sperm count, motility and morphology of sperms should be taken into account and not one single factor

REFERENCES

- 1 CAREY W H & HOTCHKISS R S *J Am Med Ass* 102 (1934) 587
- 2 ERICA WACHTEL *Recent Advances in Clinical Pathology* J & A Churchill Ltd, 1947
- 3 HOTCHKISS AND EASTMAN : *Fertility in Men* Wm Heinemann 1944
- 4 POLLAK O J & JOEL C A *J Am Med Ass* 113 (1939) 395

VENEREAL DISEASES AND STERILITY

by

Dr S C DESAI, M.D., D.V.D. (Bom.)

K E M Hospital, BOMBAY

The importance of venereal diseases as a cause of sterility has rapidly diminished in the last two decades, thanks to the modern specific and rapid curative remedies. For example, Livermore in 1929 stated that gonorrhoea alone was responsible for 80 to 50 per cent of all childless marriages, and Arthur E Giles in 1929 stated that tubal disease was present in 11 per cent of all cases of sterility investigated by him. The epithet "One child sterility"—which is a tribute to gonorrhoea as a cause of sterility, was presumed to apply to those cases where the female partner acquired gonorrhoeal infection at the same union which resulted in fertilisation of the ovum. This, however, is not entirely true, many such cases being due to secondary sepsis. Both the conditions however give rise to the same pathology viz salpingitis, the impetus for the infection to travel from the cervix to the tube being provided by trauma, during parturition. If by primary sterility we mean failure of development of reproductive capacity, the venereal diseases are not to be blamed for it but they act as main or contributory factors in the production of secondary sterility. This they do by either of the four modes, viz —

(1) By temporary or permanent interference of spermatogenesis. The venereal diseases cause this, like any other systemic disease which upsets the normal constitutional balance necessary for spermatogenesis. Syphilis mainly and gonorrhoea at times act in this manner.

(2) By mechanical obstruction in the conducting channels for ova or spermatozoa. This is the most important cause of sterility due to gonorrhoea.

(3) By physical impediments to normal sex relations in cases of chronic stasis hypertrophy of genitals by syphilitic or lympho-granulomatous process. The incidence of this complication is very small indeed, and of importance only in hospital class of patients.

(4) Venereal diseases and particularly gonorrhoea also reduces the normal fertility of spermatozoa by interference in their viability or motility by chronic infection in the prostate, seminal vesicles or cervix. This statement refers mainly to gonorrhoea.

I shall confine my discussion to mention known facts relating sterility to individual venereal diseases

Syphilis and sterility—Taking the definition of sterility as "inability of childless couple to conceive", there is no reason to think that syphilis by itself is an important cause for it, in syphilitic families (Stokes) However, Meaker (1984) estimates that 28 per cent of men with a history of syphilis are sterile The latter estimates in the speaker's opinion is however too high, and is not corroborated by other available data Gonorrhœa may be responsible for a portion of sterility in syphilitic families Syphilis can become however a major cause of childless marriages amongst syphilitics due to miscarriages and neo-natal death of diseased foetus

Syphilis is responsible for sterility indirectly, by constitutional effects rather than directly Syphilis is mentioned by Tew (1989) and Burns (1940) amongst the systemic diseases which may be the cause of sterility by interfering with spermatogenesis Hamilton in 1941 found it responsible for two per cent of 488 cases of sterility which he investigated Béclaire and Francois (1988) rated syphilis as a secondary cause of sterility in three per cent of their female cases There is no observed spermicidal or ovidical effects of spirochetes, although it can be well understood that syphilitic infection can interfere with or suppress spermatogenesis or oögenesis The other modes by which syphilis can interfere with pregnancy is by direct involvement of ovary or testis and thus disorganising their function But according to Warthin (1928) syphilis of the ovary is virtually unknown Gellhorne has reported one case of gumma of the ovary, which is a single exception to the general absence of report of this condition in the literature It is also a well known fact that manifestations of syphilis in females are singularly mild, and that pregnancy has also a beneficial effect on the course of maternal syphilis But, in contrast, the male is not so beneficially favoured by nature, and gumma of the testis or bilateral orchitis are well known, though not too common, complications of tertiary syphilis Syphilitic orchitis causes total disorganisation of the glands The fact that the loss of testicular sensation is an important diagnostic sign of the gumma of the testis, is itself an indication of severe destruction and functional impairment of this structure The damage to the testis by this condition may not be permanent in all the cases as is indicated by Hagner (1925) who reported restoration of spermatogenesis in a case of bilateral gumma of testis after treatment, Adequate reports on this important problem are not available in literature to draw final conclusions

There are very few reports, again, of structural abnormalities of spermatozoa due to syphilis One such report is by Widakowitch and other by Lane-Roberts et al The latter observers reported teratozoospermia (meaning abnormal head forms in more than 20 per cent of sperms counted) which they attributed to syphilis

Syphilis is almost never a cause of blockage in the conducting channels in either sex, excepting temporarily in cases of syphilis of the cervix, or sometimes permanently due to stenosis of cervix following a resolving gumma It is also rarely a cause of sterility by physical impediments to normal coitus due to chronic-persistent stasis hypertrophy of genitals in both the sexes

Gonorrhœa and sterility—This disease by far is the most important cause of sterility due to venereal diseases. It does not usually do so by affecting the spermatogenesis, except temporarily like any other infection. It however causes sterility by two important mechanisms, viz (1) by physical blockage and (2) by maintenance of chronic infection in the prostate, seminal vesicals and cervix, which affects the viability and motility and hence the fertility of spermatozoa.

Gonorrhœal epididymitis is the most important single cause of male sterility. This is brought out very vividly by Benzer's observation on German soldiers, so often quoted by all the text books. He found that 10.5 per cent of the patients who had suffered from gonorrhœa had no children (same as in general population and not possibly primarily due to this disease), as against 28.4 per cent of those with unilateral epididymitis and 41.7 per cent of those who had bilateral involvement. Reid quoted the incidence of sterility after bilateral epididymitis at 56 per cent (96 out of 167 cases), and Frank reports as high as 94 per cent (802 out of 842 cases). The incidence of epididymitis in patients suffering from gonorrhœa used to be 10 per cent, and thanks to the modern specific remedies it is less than 0.1 per cent now. The main prevention of this complication lies in early specific treatment, and avoidance during acute stage of the disease, of physical and physiological trauma like severe exertions, full bladder, alcohol and sexual excitement. The last four factors are recognised pre-disposing causes of extension of gonococcal infection to the epididymis. There is however a definite chance of restoration of the patency of the epididymis on the resolution of the disease, as is proved by the above figures of incidence of sterility. Gonorrhœa almost never causes blockage of the vas-deference. It is known to cause temporary blockage of the ejaculatory ducts in some cases, due to co-existent prostatitis. As a rule, their patency is restored when the prostatic inflammation has cleared up, but in some cases a permanent stenosis is left behind. The latter diagnosis should be considered if the history, clinical examination, repeated seminal examinations, and testicular biopsy suggest an obstruction which is not found in the epididymis or vas-deference. Lastly stricture of the urethra may also act mechanically to cause sterility by preventing the semen to come out.

Much less frequent, but not the least important, are cases of chronic prostatitis or seminal vesiculitis as a cause of male infertility, where viability of the sperm and their motility is impaired due to unfavourable surroundings. The prostatic infection is not however a cause per se of infertility and this is evident by the observed presence of this condition in patients with children, and by the presence of sperm in their prostatic secretions. It can become a contributory factor in some cases by causing asthenozoospermia. Hence in all cases of sterility, where there is a history and evidence of prostatic infection, this complication should be eradicated by treatment. I have observed several such instances in my experience.

Gonorrhœa in the female also interferes in the fertility in an identical manner, viz., in the blockage of the tubes which are anatomical counterparts of the vas and the epididymis in the males, and by inhibiting the ingress of spermatozoa to the tubes by presence of chronic cervicitis. Again most of the remarks made above have a parallel application to

the female cases The complication of salpingitis has become a rarity these days, with availability of specific treatment Gonorrhœa was responsible for 60 per cent of all cases of salpingitis formerly, which figure does not stand true to-day The infection is primarily endosalpingitis, the infection travelling to the tube from the cervix via endometrium of the uterus without affecting the latter. In milder cases complete or almost complete resolution takes place The chronicity in many cases is maintained by repeated re-infection of the tube The clearing up of the focus of infection in the lower genital tracts, avoidance of the physical and physiological trauma and treatment of the infected partner are important measures to remember in avoiding the exacerbations In severe cases even the first attack may bring about complete blockage of the tube Chronic cervicitis is not necessarily associated with sterility In some cases conception does not occur until the condition is effectively treated No spermatozoa may be found in the cervical canal after intercourse in some cases of chronic cervicitis with excessive mucous formation and altered pH reaction

Finally other diseases like Lympho-granuloma Venereum, Granuloma Inguinale and Chancroid are rarely causal factors of sterility, except in a minor contributory way In conclusion, the incidence of sterility due to venereal diseases is remarkably reduced due to modern remedies, and the main problem now is prevention rather than subsequent cure of this complication

Critical Notes and Abstracts

SEVEN-DAY CURE FOR ALCOHOLISM by LEON BRUEL AND RAOUL LECOQ

From Paris comes this Magazine Digest—a new type of injection treatment that actually removes the craving for alcohol

The chronic alcoholics—that large group of people for whom there has been no reliable cure, but only continued relapses into drunkenness, can at last lead normal, sober lives

This is the authors' first announcement of the development of a new and radically different method of treating alcoholism. This method does something which as far as one can ascertain has never before been attempted, it uses intravenous injections of alcohol to offset the alcohol taken by mouth. The result is a removal of the toxicomania, in other words, the craving for alcohol is ended

Realizing that the authors might be accused of raising hopes falsely, they waited for more than seven years before making this announcement—just to be sure that the treatment has a lasting effect. Alcoholics who took this treatment at their clinic as long ago as 1940 are still "cured." They are leading normal, useful lives and have no desire to return to drinking.

The authors are making no attempt to commercialize on this treatment. Full information about this simple, inexpensive cure is hereby offered to alcoholics and to physicians everywhere. The treatment takes only a week and does not harm the patient's health, in most cases he doesn't even have to go to the hospital.

There are two reasons why the affliction is hard to cure: (1) it is an illness, like diabetes or uremia, (2) it is also a toxicomania—an addiction to a drug, similar to an addiction to morphine or cocaine.

It is this second factor that makes the "cured" alcoholic slip back into another drinking bout. Even the smell of rubbing alcohol in a hospital, or the taste of a drop of wine at a banquet can start up the craving and send him on another "lost week end."

When the alcoholic tries hard to overcome his failing, with the help of psychotherapy and social workers, he is fighting an uphill battle. At any time—even after years of abstinence—some incident may revive a memory, pulling the trigger mechanism and his body overwhelms his mind in its lust for drink.

When the authors began their researches on alcoholism, they knew that this was the problem to solve, alcoholism could never be properly cured until physicians found some way to remove the toxicomania from the body.

As it happened, they found the missing link in their researches quite by accident. Here is the case, from the beginning.

The husband of a tavern keeper, wounded in World War I, had in his left lung an opaque foreign body. Because he had been discharged as a medical case, he was under observation by the Social Hygiene Dispensary of Saint-Germain-en-Laye, France. His work as horse dealer led him to frequent country fairs, where transactions were celebrated with drinking parties.

After one such spree, he had some trouble with his boss and lost his job. Upset, he went home to the tavern and went to bed. He asked for wine, but his wife refused to let him have any.

So he left home and went to the dispensary, where he complained of back pains on his left side, near the spinal column, of fever, of sweats, and hemoptysis. The doctor at the dispensary didn't know the patient's addiction to alcohol. He x-rayed the man's lungs and, noting the shadow in one lung, attributed the entire trouble to a lung abscess.

The patient was then sent to the authors for treatment for lung abscess. Like other patients with similar lung complaints, he was treated by the Landau method, which consists of injections of ethyl alcohol in a sodium chlorinated solution.

(This patient, of course, was really suffering from the early stages of delirium tremens. However, because there was no smell of liquor on his breath, the other symptoms—the abundant sweating, extreme nervousness, and high temperature, plus the x-rays of his lungs—seemed to confirm the diagnosis of lung abscess. He was incapable of standing up, muttered incomprehensible words, trembled with all his body, and slept badly.)

The first night, this patient was given 40 c c of alcohol by injection, then each day for the next week, 20 c c in the morning and 20 c c at night.

The change in him was amazing. In 48 hours the trembling, fever, sweats, insomnia, and speech difficulties disappeared.

The family now appeared on the scene, and revealed his history of alcoholism.

By the fourth day, the d t's had completely disappeared, and the patient was discharged. He was apparently none the worse for his experience, and seemed to have no immediate craving for alcohol.

The authors were amazed that injections of ethyl alcohol should coincide with such a rapid recovery from delirium tremens, and they determined to repeat the treatment whenever a similar case should come up.

Some days later, a chronic alcoholic went to their clinic, his body was bathed in sweat, he was running a fever, and he suffered from hallucinations. They injected into his veins some ethyl alcohol. And, just as in the first patient, the fever, trembling, sweating, and hallucinations disappeared within 48 hours.

A third d t patient was brought to them in a strait jacket. He was a 40 year old farmer whose alcoholic abuses were well-known. The medical certificate said "Acute delirium in an inveterate alcoholic." He was given ethyl alcohol injections, and the results were the same as in the preceding cases. When his wife and children visited him on the third day, to their amazement he talked to them as if nothing had happened. On the tenth day, he was able to go home.

So far, they had tried the injections only as a means of clearing up delirium tremens. They decided to follow up subsequent cases, to see if the injections could bring about a lasting cure. The treatment using alcohol to cure alcoholism didn't seem to make sense. Nevertheless, there was no denying that the treatment worked. It also speedily cleared up the liver and circulatory trouble which went with the d t's.

Their next patient was a gardener with all the signs of chronic alcoholism—insomnia or nightmares, loss of appetite, tremblings, &c.

For some time past, this man's character had been changing. Once very regular in his work, he gradually abandoned most of the gardens in his care, became ill tempered, and constantly quarrelled

with his family. When brought to the hospital by his wife he was in a drunken state, and she insisted that he be kept in hospital. He refused and had to be detained by force.

At first his condition grew worse. His temperature rose, and hallucinations increased. He was given injections of ethyl alcohol, 30 per cent, twice a day. After 60 hours' treatment, the acute crisis disappeared. After eight days of treatment, the patient was ready to leave.

An understanding employer gave him back his job. Once more he became industrious, conscientious, eager to take on extra tasks. In following up the case, we made him realize that his illness was due to alcohol. He promised to reform. Most ex-alcoholics do make such promises, but this man kept his word. The craving, he told us, had gone.

Seven years have passed since then, and there has been no relapse. Happiness has returned to his home. How does the alcohol injection treatment work?

At first such a treatment seems paradoxical. When the authors approached the director of a research institute, asking him if such a method had ever been tried before, he replied: "Nobody has yet thought of injecting alcohol into the veins of patients who are already saturated with it."

During their researches the authors finally came across what seems to be the explanation. They proved that the intermediary products of alcohol metabolism acidify the organism.

The first tests were made with rabbits, which were given 5 c c of alcohol, diluted with an equal volume of water. "Less than two hours after each rabbit had been given this alcohol by mouth, there was a fall in the alkali reserve of the blood."

From then on, they tried to find out if alcohol did the same thing to humans. They found that there is a close connection between the decrease in the body's alkali reserve and the intensity of delirium. This, strange as it may seem, shows that alcoholism is really a disease in the class of diabetes—in the diabetic, a drop in the alkali reserve brings on the coma.

Take the case of Private D. A. Chronic alcoholic, with an enlarged liver and the beginnings of blocked circulation, he fell down the barracks stairs. The ensuing shock brought on delirium tremens, during which he became insubordinate. He was imprisoned.

At first considered a malingerer, he was not brought to the hospital until after 24 hours of delirium. Then, laboratory tests showed that his alkaline reserves had fallen to a very low figure. Also, his condition had become complicated with heart and liver trouble.

Nevertheless, as the alcohol injections were given, the alkaline reserve in his body slowly increased. For five days, the confused state, insomnia, and fever persisted. By the tenth day, the alkaline reserve had risen to 57 c c. His delirium had gone, his liver and heart functions were back to normal. He returned home, completely well. What happens is, therefore, this: Alcohol taken by mouth has an acid effect, thus reducing the body's alkalinity. But when injected into the veins, alcohol has precisely the opposite effect—it is alkaline, offsetting the acid effect of alcohol taken by mouth.

The following case gives a detailed analysis

A 38 year-old government clerk was brought to the hospital in a strait jacket. The medical certificate emphasized abuse of fermented beverages. In one bout he had taken three quarts of wine, plus black coffee mixed with additional wines, and various liquid "Appetizers"

Delirium tremens had begun two days before. He was running a fever, and was completely unconscious. His urine was scanty, and dark in colour. He had abundant sweat, his breath was fetid and acetone, The blood analysis showed that the alkaline reserve was down to 88 c c per 100

Intravenous injections of ethyl alcohol were begun immediately. Two hours after the first injection, the alkaline reserve had risen to 40 c c. Then a gradual rise occurred. 43 c c on the second day, 45 c c on the fourth day and 57 c c on the eighth day.

As his alkaline reserve was restored, his mental troubles disappeared. On the second day, the patient, without fever or hallucinations, could be placed in a general ward. His urine was back to normal. On the fourth day, he was quietly reading his newspaper. He now devoured his food and slept soundly.

On the tenth day, when he left the hospital, he had no more signs of alcoholism.

If overcoming delirium tremens merely involves restoring the body's alkaline reserve, why isn't it possible to do this by some means other than alcohol injections?

The authors tried intravenous injections of a 10 percent solution of calcium gluconate, which also bring about an increase in the alkaline reserve of chronic alcoholics. But this treatment did not prevent delirious crises or hallucinations.

The authors believe that, although other chemicals may restore the body's alkaline balance, only injections of ethyl alcohol can bring about the detoxication of the chronic alcoholic. Only alcohol, injected into the veins, makes possible the desensitization—curing the "trigger action" which otherwise binds the alcoholic to his mania.

It is not necessary to wait for a serious crisis before beginning the treatment. The intravenous alcohol treatment is just as efficient when the chronic alcoholic is sober. When carried out according to the dosage and methods they have developed, it can be given safely at any time. About the only complication is a certain amount of hypertension, which is counteracted by intramuscular injections of vitamin A.

However, the treatment does not bring about a permanent cure unless the patient stops abusing alcoholic beverages. For, even though he is cured in a physical sense, he can again—just like anybody else—drink enough to bring back his craving and again become an alcoholic.

For this reason, any mental factor—such as a feeling of inadequacy, a desire to escape from worry—which may have caused excessive drinking in the first place should be cleared up. Then, because the alcoholic has been successfully freed of his craving there is no reason why he should not stay away from liquor.

Going one step further, the authors state that their treatment can be used as a preventive of chronic alcoholism, even among those who insist on continuing their drinking.

For example, a man who normally drinks from 15 to 20 quarts of wine in a week is given injections of 700 c c of ethyl alcohol during

the same period. In other words, two quarts of absolute alcohol taken by mouth are offset by 175 c c of the same product taken in the veins. As Lecoq, Chachard, and Mazous showed in experiments with rabbits, the same dosage of alcohol which intoxicates when taken by mouth eliminates all nervous signs of alcoholism when injected intravenously.

Approaching the problem of bodily acidity from another angle, all chemicals which create anionic gases in the stomach should be effective in warding off drunkenness. They have proved this with a very pure carbonate of a kind rarely found in the market. One of their interns takes a good supply with him whenever he goes to a party, and thus maintains a light stomach and a clear mind throughout the evening.

Thus the fight against alcoholism now results in victories at every state. Drunkenness can be prevented in the very place where it is produced by taking tablets which neutralize the immediate effects of alcohol. Nervous forms of alcoholism, and the latent forms of concealed alcoholism, can be treated by combinations of B-complex vitamins.

Finally, the extreme cases of delirious and hallucinatory chronic alcoholism, resulting from a definite toxicomania, can be cleared up with intravenous injections of ethyl alcohol, with glucose and hepatic extracts.

For the benefit of doctors, here is additional data. The authors have definitely adopted for their patients the total dosage of 700 c c of 25 per cent ethyl alcohol, combined with glucose and hepatic extracts. The injections are given intravenously, daily, in the following dosage:

1st day—180 c c in two injections (morning and evening, 90 cc + 90 cc),

2nd day—150 c c in two injections (75 cc + 75 cc),

3rd day—120 c c in two injections (60 cc + 60 cc),

4th day—100 c c in two injections (50 cc + 50 cc),

5th day—50 c c in one injection,

and, 6th day—50 cc in one injection, making a total of 700 cc of 25% ethyl alcohol (175 cc ethyl alcohol + 525 cc dist water)*

CAUSATION IN ALCOHOLISM

A recent study of causation in alcoholism by Bird states that many factors direct and subtle, influence the fate of the alcoholic, such as heredity, physical constitution, physical deficiency or disease. Alcohol deadens the senses and is therefore used by the alcoholic to escape the intensity of reality and its restricting influence. Other methods of escape may be considered more respectable, but are not necessarily less destructive. Addiction to work hobbies, mental and physical ills may have as serious effects as alcohol upon other personalities that escape by such means.

Civilization has for the main part brought an end to the need for primitive aggressiveness as a protection against external reality, due to this man has become more introspective, and it is against internal reality that man must protect himself. Man's internal reality consists of all his primitive characteristics—uncontrolled sexual desire, aggres-

* I have treated with intravenous ethyl alcohol one patient with Delirium Tremens following an acute alcoholic episode according to the method described by Bruel and Lecoq with spectacular recovery. But it is difficult to give a definite opinion about this new method of treatment because of spontaneous recovery in cases of delirium tremens episodes in from three to seven days.—N. D. PATEL

siveness, selfishness, cruelty and a wish to be self-sufficient and independent. It is this internal reality that man finds intolerable and from which he may seek escape through alcohol.

The author considers the fellowship in Alcoholics Anonymous and its social aspects an important part in rehabilitating the alcoholic. To one who has lost his friends and interests, A. A. gives the opportunity to revive such contacts and to transmute his preoccupation with himself into an interest in others.

Child training is also stressed. A child at birth is completely selfish, aggressive and sexually uninhibited. He knows no modesty, no shame, no restraint. It is only through the constant pressure from parents and society that he is forced to change. If he is taught mercilessly that all sex and all aggression are bad, the child will grow up with an ever-present terror within himself of his sexual and aggressive desires, a terror which he will not be able to control or understand; he will be forced to escape through alcohol, neurosis, ulcers, high blood pressure or suicide.

Psychiatric study of alcoholics always leads directly back to the patient's childhood and it is there that the first causes are found. Therefore, the prevention of alcoholism can only come through improved child training and those who are interested in alcoholism should add their support to programs that promise better opportunities for children to grow up healthily.

(Bled Brian Cleveland, Ohio. One Aspect of Causation in Alcoholism, Quarterly Journal of Studies on Alcohol 9: 4 March 1949.)

PROVISIONAL DEFINITION OF POLIOMYELITIS VIRUS

Confusion regarding restrictions that should be applied to the term poliomyelitis virus, as opposed to other allied terms such as encephalomyelitis or encephalitis virus, has recently been considered by the Committee on Nomenclature of the National Foundation for Infantile Paralysis. Recommendations submitted were that the term poliomyelitis virus be used only to designate strains of the agent originally described as the cause of poliomyelitis in man, regardless of the source from which it may be recovered in nature. The identifying characteristics of this virus are the production of typical experimental disease in the monkey, the characteristics and distribution of histologic lesions in the spinal cord and brain of primates, the host range of the virus and its immunologic properties.

The clinical signs of disease in monkeys include fever, tremor and spasticity of muscles, usually followed by paralysis within a day or two. Severe generalized tremors are considered almost without exception to be pathognomic of poliomyelitis. Pathologic lesions in the monkey essentially duplicate those in human beings in type and distribution. Spinal cord lesions are concentrated in the gray matter and primarily in the anterior horn cells. These are accompanied by focal and diffuse infiltration of leukocytes in areas of nerve cell damage. The cerebral cortex is noted to be generally spared and the deep cerebellar nuclei are generally involved.

Virus which produces the characteristic experimental disease in monkeys but does not infect other mammals may be considered poliomyelitis virus. In addition, certain strains isolated from typical cases have the capacity of producing paralytic poliomyelitis in mice, hamsters and cotton rats, but not in guinea pigs or rabbits. These strains appear to be immunologically related to the Lansing—1938 strain.

The committee stated that certain strains of encephalomyelitis virus of mice or "mouse poliomyelitis" (e g, TO, FA, GD VII) and other viruses that produce lesions in the anterior horns of spinal cords in experimental animals but that do not otherwise satisfy criteria set down for poliomyelitis virus, should not be called "poliomyelitis virus," "mouse poliomyelitis virus," or "poliomyelitis like virus."

(Editorial: Provisional Definition of Poliomyelitis Virus. *Journal of the American Medical Association* 139: 852 March 1949. Committee on Nomenclature of the National Foundation for Infantile Paralysis. A Proposed Provisional Definition of Poliomyelitis Virus, *Science* 108: 701-705 December, 1948.)

REACTION OF THE BODY TO POLIOMYELITIS

The established principles regarding the etiology, pathogenesis and pathology of poliomyelitis were discussed recently in an article by Guyton. The author deferred to personal experience as a patient with poliomyelitis in explaining several poorly understood symptoms. It postulated that the pain, tenderness and muscle shortening are probably due to a generalized vasospastic condition secondary to lesions in the medulla. The prevalence of poliomyelitis in the United States has greatly increased in the last few years, and it has been observed that as sanitary conditions have become better the prevalence of poliomyelitis has increased and relative incidence among older persons has risen.

It is explained that there is considerable cross immunization between poliomyelitis and other diseases. Therefore, as the other diseases are conquered, many of the immunizing antigens of childhood being removed, the body is left susceptible to poliomyelitis. Patients with poliomyelitis suffer markedly different involvements of the nervous system and different patterns of paralysis depending on the virulence of the virus and the susceptibility of the patient. Although in practically all cases of poliomyelitis there are lesions throughout the brain as well as in the spinal cord, there is little permanent damage except to the anterior horn cells.

The paralysis of poliomyelitis is considered flaccid in nature and due to actual death or inactivation of motor nerves from the spinal cord to the muscle. Disturbance of the medullary sympathetic centers is a possible explanation as to why shortening and pain often occur in muscles which are not paralyzed. Shortening occurs in all muscles which have pain regardless of the amount of paralysis present. The same agents which relieve pain also have a beneficial effect on the shortening process which indicates a common vasospastic origin of the two phenomena.

Recovery from the paralysis of poliomyelitis may be divided into three phases: first, recovery in the spinal cord; second, recovery of the peripheral nerves; and third, recovery of the muscles. Insofar as proved data exists, it appears that recovery in the spinal cord takes place within the first two months or not at all. Other changes taking place in the cord after this time have been postulated but thus far remain entirely hypothetical. Such is not true of recovery of peripheral nerves and muscles, for there is much physiologic data indicating that these recovery processes may extend for several years.

The recovery of nerves may occur by two processes: first, the regrowth of axons from nerve cells which have not been killed but from which the axons have been destroyed; and second, by an arborization of axons which are still present. The process of recovery by axonal arborization proceeds rapidly for the first few months because of intra-

muscular because of aborization at higher levels. The recovery in poliomyelitis, therefore, does proceed rapidly for the first few months and then slowly for several years. Happiness and the will to live are usually restored to the patient when he has been offered security and his way of life has been repatterned not to require the physical abilities which no longer exist.

(Guyton Arthur C. Department of Pharmacology, University of Mississippi: Reaction of the Body to Poliomyelitis and the Recovery Process. *Archives of Internal Medicine* 83: 27 January, 1949.)

MENTAL HEALTH AND INTERNATIONAL TENSIONS

Members of the UNESCO Conference on World Tensions and the International Congress on Mental Health have recently reported deliberations of major significance to world peace. The conclusions are based chiefly on the psychiatric premise that human emotions ("human nature") can now be scientifically studied, understood and even changed both for the individual and the group. Wars are unnecessary and are not considered inevitable consequences of human nature. Some needs are vital to all men—these include freedom from disease, insecurity and fear. Men everywhere desire at the same time fellowship, respect of their fellowmen and a chance for personal growth and development.

Inequalities in the use of modern productive power and resources were considered partially responsible for economic inequalities, insecurities and frustrations which lead to group and national conflict. One group may be wrongly led to see another group as a menace through acceptance of false images and oversimplified solutions. Myths, traditions, and symbols of national pride handed down from generation to generation, plus current social and nationalistic symbols are believed to hinder free movement of thought across artificial political boundaries of an interdependent world. The report suggests that neither continued colonial exploitation nor oppression of minorities is compatible with world peace.

As general standards of mental health are not universally applicable, a universal recommendation for the provision of types and numbers of psychiatric hospitals and clinics per unit of population cannot be made now. The primary concern of workers in the field of mental health is the development of methods for the release of human potentialities individually and collectively for the common good.

This newly clarified concept of the modifiability of human nature through insight into otherwise unconscious obstructions suggests ways of removing obstacles to personal and social development. The primary factors leading to better mental health are the acquirement by the individual of self-knowledge and group social insight. Effort in behalf of one's own group can become compatible with effort in behalf of humanity generally.

(*Internal Mental Health and International Tensions, Journal of the American Medical Association* 139: 852 March 28 1949. UNESCO Conference on World Tensions—An International Multidisciplinary Group. *Psychiatry* 11: 231-233 August 1948. International Congress on Mental Health, London, August 1948. Statement by International Preparatory Commission. *Psychiatry* 11: 235-261 August, 1948.)

RETROGRADE ARTERIOGRAPHY IN CARDIOVASCULAR LESIONS

In a recent paper by Freeman and Miller, the development of their use of retrograde arteriography is shown in the visualization of lesions of the aorta and of peripheral vessels. Retrograde arteriography has been used in 11 patients for visualisation of vascular lesions involving

the peripheral arteries, and the abdominal and thoracic aorta. Although arteriography can best be accomplished by the injection of radio-opaque material into the artery proximal to the lesion to be studied, occasionally the location of the lesion or its character makes it difficult to carry out this technique.

Under such circumstances, retrograde arteriography may offer a method for adequate visualization. Attempts at visualization of the abdominal aorta have not been successful by the authors, except in the patient in whom the catheter was introduced through a cannula inserted into the femoral artery. It has been shown by Farinas that to be successful fluoroscopically, the injection must first overcome the inertia of the blood flow and, second, must overcome the blood pressure. According to this, it may be that injection of a larger quantity of solution under higher pressure would have yielded more satisfactory results, however, the danger of thrombosis at the site of injection is very real, specially where a large needle is inserted into a small artery. This thrombosis occurred in three of the 11 patients, although distal ischemia was not produced.

With the use of 70 per cent Diodrast, the possibility of serious systemic reaction should be considered, especially when there is any opportunity for the contrast medium to enter the cerebral circulation. Retrograde arteriography was successfully used in all but four of the 11 patients in whom it was difficult or impossible to introduce the radio-opaque substance into the artery proximal to the lesion.

(Freeman Norman E. M.D. San Francisco Calif. and Miller Earl R. M.D. Retrograde Arteriography in the Diagnosis of Cardiovascular Lesions. I. Visualization of Aneurysms and Peripheral Arteries, *Annals of Internal Medicine* 30: 330 February 1940. Farinas P. L. A New Technique for the Arteriographic Examination of the Abdominal Aorta and Its Branches. *American Journal of Roentgenology* 41: 641 1941.)

206

MISCONCEPTION CONCERNING THE Rh FACTOR AND INTERRUPTION OF PREGNANCY

The authors report two cases illustrating the danger of interrupting pregnancy in the immunized Rh-negative woman because of the history of previous erythroblastotic children and the supposed homozygosity of her husband. The first case showed a rather definite increase and qualitative change in antibody titer, which in the minds of many investigators are indications of active immunization. As an anti-d serum was not available to the authors, the genotype of the Rh₀ (DeE) husband, in reference to the clinically important D antigen, could not be determined.

Although the chances were in favour of another Rh-positive child, on the basis of the first Rh-positive child, the second erythroblastotic and undoubtedly Rh-positive child and the rising antibody titer, this pregnancy terminated in a live-Rh-negative infant. In the second case the antibody titer rose and slowly fell during the pregnancy, regaining a somewhat higher level six weeks after delivery. The husband's genotype was erroneously determined as homozygous, on this basis, as well as on that of the history and the antibody titers, interruption of pregnancy was strongly suggested, and sterilization was actually carried out. Both cases show an increase and a qualitative change in anti-Rh-antibodies, despite an Rh-negative product of conception.

This stimulates closely the phenomenon of nonspecific anamnestic reaction. Although attention was called to this phenomenon by several authors throughout the literature on the RH factor, its existence was seriously questioned recently by other investigators. The opinion

expressed in this article ascribed such a reaction to "the intrinsic inaccuracies of titration methods" However, in the cases reported here the titrations were checked by multiple methods and the height of the titers almost preclude gross error

In each case physicians favoured interruption of the pregnancy, an opinion based on serologic date In the second case the authors neglected to check the anti-c reaction of the husband at an early date Had this been done, confusion by an erroneous laboratory report could have been avoided Cautious interpretation and careful recheck of the serologic results in all cases of Rh sensitization, and particularly in those involving the zygosity of the husband, are urged

(Kendig Edwin L Jr Richmond Va, and Waller Robert K A Misconception Concerning the Rh Factor and the Interruption of Pregnancy *American Journal of Diseases of Children* 76 689 692 December, 1948)

AMINO ACID AND ENERGY UTILIZATION

Simultaneous nitrogen balance and energy metabolism studies were conducted by the authors on adult rats receiving amino acid mixture in a diet otherwise very low in nitrogen Each amino acid diet period was preceded by a 7-day depletion period in which an isocaloric N-free diet was fed The diets were administered by stomach tube twice daily in order to insure equal intake by every animal every day

Resting energy metabolism determinations were made during a 10-hour period on the last day of the amino acid diet and again two days later after a fast of 36 hours The difference between these rates was taken as representing the specific dynamic action of the diet When a "complete" amino acid mixture simulating whole egg protein was fed the N balance index was invariably greater than unity. The N requirement for maintenance on this amino acid mixture averaged 162 mg N/day/kg^{3/4}

In six experiments with two groups of rats the maintenance N requirement proved a more consistent characteristic of the amino acid mixture than the N balance index Reducing the DL-isoleucine to one-third the quantity in the "complete" amino acid mixture caused a decrease in N balance index, an increase in maintenance N requirement to 212 mg N/day/kg^{3/4}, and an increase in specific dynamic action of 3 Cal/day/rat A similar reduction in DL-methionine caused a decrease of N balance index to about half an increase of maintenance N requirement to 323 mg N/day/kg^{3/4} but no significant change in specific dynamic action Reduction of DL-valine to one-third the quantity in the "complete" amino acid mixture caused no significant change in either N utilization or energy metabolism

Substituting glycine for glutamic acid caused no significant change in N balance index maintenance N requirement or specific dynamic action Reducing the quantity of an essential amino acid will, if carried far enough, lead to decreased efficiency of utilization of N (decreased N balance index and increased maintenance N requirement), and probably to a parallel decrease in efficiency of energy utilization (increased specific dynamic action) Such a decrease in efficiency of N utilization was found when either isoleucine or methionine was reduced to one-third The corresponding decrease in efficiency of energy utilization was found only in the case of the low isoleucine diet

(Anderson Joseph T Rochester New York and Nasset F S Nitrogen Balance Index and Specific Dynamic Action in Rats Receiving Amino Acid Mixtures Low in Isoleucine Methionine or Valine *Journal of Nutrition* 36 703-720 December, 1948 Dr. Anderson is associated with the

Department of Physiology and Vital Economics, School of Medicine and Dentistry, University of Rochester)

EPINEPHRINE SHOCK

A case of pheochromocytoma which terminated fatally after "epinephrine shock" was recently reported in an article by Ferraro and Angle. Although the clinical syndrome associated with pheochromocytoma of the adrenal gland is well recognised, in some instances, medical aid is not sought until the terminal fulminating episode, during which the patient may present a variety of symptoms which tax the ingenuity of the most astute diagnostician. Such was the nature of the case presented.

A 32-year old soldier, assigned to duty in India, became suddenly ill with complaints of palpitation, dyspnea, epigastric pain, nausea and vomiting. Several hours later, he appeared pale and drenched with perspiration. The epigastric pain persisted, but was alleviated somewhat by changing positions. The temperature was 100.2°F, the pulse rate 120 diastolic. Widely dilated pupils were observed which reacted sluggishly to light. There were moist rales through the lower lobes of both lungs. The heart rate was rapid and regular. A mottled cyanosis of the extremities was conspicuous. Abdominal examination revealed nothing significant.

On his admission to the hospital, 0.082 Gm. of morphine sulfate was administered hypodermically, external heat applied to the body and oxygen therapy was instituted continuously. By 7 P.M. the day the temperature reached 104.2°F and the pulse rate barely perceptible, 156. In view of the unexplained temperature, 50,000 units of penicillin was administered. However, shallow respirations, progressive cyanosis and a temperature of 106.4 developed. Death occurred 14 hours after the onset of his symptoms.

The laboratory data were as follows. The red blood cell count was 6,800,000 and the white blood cell count 20,000 with 82 per cent polymorphonuclear cells, 8 per cent lymphocytes and 10 per cent monocytes. The electrocardiograph showed a rate of 122 and a QRS wave of 0.08 seconds. The QRS wave was interpreted as indicating left axis deviation and sinus tachycardia. Autopsy revealed that a large encapsulated tumour conspicuously occupied the position of the left adrenal gland and measured 7 by 5 by 4 cm. It weighed 70 Gm. Microscopic examination revealed a diffuse proliferation of normal-appearing chromaffin cells surrounded by a delicate fibrous stroma in which occasional dilated capillaries were noted. The syndrome during an "epinephrine crisis" was thought to result from an abnormal release of epinephrine into the general circulation. In view of the paroxysmal nature of these attacks, it was assumed that during the interim state of well being the release mechanism is held in abeyance.

(Ferraro Louis R. M.D. Poughskeepie N.Y. and Angle Robert G. M.D. Pheochromocytoma with Symptoms of Epinephrine Shock. *Archives of Internal Medicine* 81: 793-798 June, 1948.)

SILENT GALLSTONE A 10 TO 20-YEAR FOLLOW-UP STUDY OF 112 CASES

Since the advent of cholecystography, the problem of the silent gallstone has become an increasingly important one, several pertinent questions are being asked. How often are gallstones silent and how often is the physician confronted with the problem of the silent gallstone? What advice should be given to the patient who has silent

gallstones? Should he be told to undergo cholecystectomy or should he be told to await development of dyspepsia or colic before submitting to surgical treatment? Should he be urged to undergo cholecystectomy after the first attack of colic or after several attacks have occurred?

Reviewing the literature, Comfort and his associates found wide divergence of opinion and a lack of accurate data on the problem of the silent gallstone. In the hope of supplying some of the data not now available but necessary for decision regarding treatment of the silent gallstone, a long-term follow-up study of all cases in which gallstones were found incidentally during the course of some other abdominal operations at the Mayo Clinic was carried out.

The records of 998 such cases occurring from 1925 through 1934 were reviewed. Approximately one-half of these were discarded as unsuitable for long-term follow-up because the operation had been for cancer. Many others, including those with duodenal ulcer, were discarded because some of the abdominal symptoms might have been due to the cholelithiasis. Follow-up letters were sent to 184 persons. Replies were received from 115. Each patient was asked if indigestion or colic had preceded the discovery of the gallstones and several replied that symptoms had been present, so that these, too, were discarded. Finally, 112 cases were considered suitable for study. The average age of the 112 patients was 84.2 years when the gallstones were discovered.

It was found that in 61 cases symptoms did not develop. In the 51 cases in which symptoms occurred, 30 patients complained only of dyspepsia and 21 experienced painful seizures. Five of the 21 patients experiencing painful seizures also had jaundice.

Cholecystectomy may be advised but need not be urged, if the patient prefers to accept the chance of experiencing painful seizures or the increased risk of surgical treatment in the event the complication of calculous disease of the biliary tract appears.

Many patients will prefer to have gallstones removed in order to eliminate the threat of painful seizures or severe complications. Others, knowing the higher risk of surgical intervention should complications develop, will prefer to take the chance that no symptoms will develop. Surgical treatment of the silent gallstone may be classified as optional or elective surgery, but surgical intervention should not be postponed after symptoms, and more especially after attacks or colic, appear.

(Comfort M W., Rochester, Minn., Gray, H K and Wilson J M.: *Annals of Surgery* 128: 971-977 November, 1948. The authors are connected with the Divisions of Medicine and of Surgery, Mayo Clinic Rochester.)

CARCINOMA OF THE STOMACH

Moore and his associates direct attention to Schindler's belief that the prognosis and perhaps the advisability of any therapeutic procedure for carcinoma of the stomach may be based upon the Borrmann type of the tumor. Borrmann separated the gastric carcinomas into four gross types: I, sharply demarcated polypoid carcinomas; II, sharply demarcated ulcerated carcinomas; III, partly infiltrating carcinomas; IV, diffusely infiltrating carcinomas. Combining types I and II as "limited" and types III and IV as "infiltrative" groups, Schindler noted that there was a much higher resectability rate and lower mortality rate for the former group. On the basis of an analysis of 289 cases Schindler believed that the patient with a limited tumor has a 10 to 13

times greater chance of a three-year cure than has the patient with an infiltrative tumor, and that for the latter no five-year-cure appears possible. On the basis of his data, Schindeler questioned the advisability of resection of infiltrative tumors.

Since this challenges the belief that as many carcinomas as possible should be resected, the authors decided to review the records of patients treated at their clinic with special reference to Borrmann types of tumors. In the period 1938 to 1948, inclusive, the diagnosis gastric carcinoma was made in 842 patients and in 177 of these gastric resection was done.

On the basis of their analysis they arrive at the conclusion that the presence or absence of demonstrable metastases in regional nodes among patients subjected to gastric resection for carcinoma has a greater prognostic value than does the Borrmann type of the tumor.

The Borrmann type affects the prognosis of groups of cases to the extent that the limited tumors provide a proportionately large number of patients free of metastases while the infiltrating tumors which are more numerous are more likely to have metastasized.

The presence or absence of metastases cannot be accurately determined preoperatively and no patient should be denied operation because of the type of tumor he may be determined to have.

(Moore, G. E. Minneapolis, Minn. State D. Hebbel, R. and Treloar, A. E.: *Surgery Gynecology and Obstetrics* 87: 513-518 November, 1948. The authors are connected with the Department of Surgery, Pathology and Biostatistics, University of Minnesota Medical School.)

SURGICAL TREATMENT AND THE PHYSIOPATHOLOGY OF COARCTATION OF THE AORTA

According to Bing and his co-workers coarctation of the aorta belongs to the group of congenital cardiovascular malformations in which arteriovenous shunts are absent, and in which there is no cyanosis. Diagnosis is not difficult in most cases if one recalls that there is usually hypertension in the upper part of the body and hypotension below. There is usually evidence of increased collateral arterial pathways in the upper part of the body, absence or suppression of arterial pulsations in the lower extremities, and notching of the ribs in the older patients. A systolic murmur may be present. The stenosis or atresia can usually be visualized by angiocardiography. The complications associated with severe coarctation include those accompanying hypertension due to other causes.

The authors review observations on 28 patients who were operated on for coarctation of the aorta. Thirteen of the patients were 20 years of age or above, while 10 were younger. An anastomosis was completed in 21 cases of the 22 in which it was attempted. In 17 cases the stenosis was resected and an anastomosis of the proximal and distal ends of the aorta was performed. In four cases in which the proximal segment of the aorta was too short for end-to-end suture, the left subclavian artery was used to by-pass the stenosis. There were three deaths, including one in a child who had multiple congenital defects which had been recognized preoperatively.

Physiologic investigations disclosed no significant deviation of the cardiac output from normal. Blood flows through the arm, which were elevated before operation, fell following surgery. The blood flow through the leg rose postoperatively. Hypertension in the upper part of the body and hypotension in the legs were observed preopera-

tively After operation, these pressures tended to equalize Analysis of the physiologic data indicated no generalized elevation of peripheral vascular resistance It is probable, therefore, that the hypertension in coarctation of the aorta is not attributable to a renal pressor mechanism, but is due to the resistance of the stenosis and collaterals.

(Bing R J Baltimore Md Handelman J C Campbell J A Griswold H E and Bialock, A Annals of Surgery 128 803 824 October, 1948 The authors are connected with the Department of Surgery of the Johns Hopkins University and Johns Hopkins Hospitals)

DISCONTINUOUS THERAPY WITH PENICILLIN

The authors made a study of the therapeutic effectiveness of discontinuous penicillin therapy, consisting of one or two daily doses of penicillin in aqueous solution Since March, 1947, this dosage schedule has been used in the treatment of 125 patients with various acute infections, including 44 patients with pneumococci pneumonia From observations thus far made, it appears that this treatment regimen provides entirely satisfactory therapy for the great majority of penicillin-susceptible infections It should be emphasized, however, that such discontinuous therapy presumably would be inadequate in the treatment of serious staphylococci infections, bacterial endocarditis and certain other rarely encountered infections which usually require large quantities of penicillin

Moreover, on theoretical grounds, it is possible that discontinuous penicillin therapy might not be the equal of intensive continuous therapy in the prevention of nonsuppurative complications of group A hemolytic streptococci infections Finally, it should be emphasized that, from the observations in two patients with pneumococci meningitis, the possibility is suggested that certain suppurative complications which occur in patients receiving continuous treatment may occur more frequently if discontinuous treatment is employed

Nevertheless, the clinical results observed in the treatment of pneumococci pneumonia and other frequently encountered infections indicate that highly effective penicillin treatment may be provided by discontinuous therapy without the rigid restrictions imposed by conventional dosage schedules and dosage forms, which are based on the concept that continuous levels of drug in the body are required More extensive clinical trial is necessary, however, to obtain a precise evaluation of the comparative value and the limitations of discontinuous therapy

(Tompsett, Ralph et al Cornell University Medical College, New York N Y Discontinuous Therapy with Penicillin Journal of the American Medical Association 139: 555 560 February 1949)

UNDECYLENIC ACID GIVEN ORALLY IN PSORIASIS AND NEURODERMATITIS

Perlman presents a preliminary report on a series of 17 patients with chronic psoriasis, both localized and generalized, who were given gradually increased doses of undecylenic acid by mouth for varying periods of time, with definite improvement in the psoriasis characterized by a disappearance of the psoriatic lesions, a permanent relief of the itching complained of and, in several instances, associated with arthropathies, a definite disappearance or improvement in the joint pains

A series of eight patients with neurodermatitis were treated with undecylenic acid by mouth for varying periods of time, with improvement or disappearance of the lesions and itching Definite claims for undecylenic acid cannot be made from the comparatively small number

of patients studied at this time. However, undecylenic acid seems to hold a great deal of promise in the improvement and possible prevention of recurrences of psoriasis and neurodermatitis. It is hoped that this study will stimulate research, clinical and scientific, on undecylenic and other unsaturated fatty acids, in all phases. Under no circumstances should it be accepted at this time as the most effective and only treatment.

(Perlman Henry H Philadelphia Pa Undecylenic Acid Given Orally in Psoriasis and Neurodermatitis Journal of the American Medical Association 139 444-447 February 1949)

HEROIN, DEMEROL, AND HYOSCINE IN LABOUR

Three routines of medication were adopted by the authors on 300 patients in the first stage of labor. The patients were divided into three groups of 100 each. Group "A" received Heroin gr 1/8 and hyoscine gr 1/150 when patient begins to mind her pains. Hyoscine gr 1/150 in one hour, and then gr 1/300 q 2-3h, p r n. Group "B" received Denterol 100 mgm and hyoscine gr 1/150, when patient begins to mind her pains. Hyoscine gr 1/150 in one hour, and then gr 1/300 q 2-3h, p r n. Group "C" received Demerol 100 mgm and hyoscine gr 1/150 when patient begins to mind her pains. Demerol 100 mgm in one hour, and then 100 mgm q 2-3h, p r n.

Of the three routines described, the heroin-hyoscine group proved to be the most effective from the standpoint of analgesia and amnesia. In many instances the authors felt that they probably could have repeated the heroin, in a smaller dosage, without any undue risk to the baby. Heroin and hyoscine, repeating the hyoscine, should not be used except in a hospital with adequate nursing supervision, because of the excitement, restlessness, and irrational behavior it may produce.

The authors state that demerol had no depressant effect on the fetus. Statistically, in the three routines described, there was no significant difference in the percentage of asphyxiated babies. However, the trend was towards more cases of asphyxia in the routine of demerol-hyoscine where the demerol was repeated. The authors suggest that the variable factors which may enter into the production of asphyxia neonatorum and are difficult to measure, such as the trauma of labor, and the final anesthetic, mild degrees of dystocia, and susceptibility to the drugs administered, may be more important than the timing of the drugs administered for sedation. There were no maternal or fetal deaths in this series which could be directly attributed to the medication used.

(Davis M M Dalhousie University Halifax, N S and Tupper W R, C Heroin Demerol and Hyoscine in Labour Canadian Medical Association Journal 60 118-119 February 1949)

STUDIES ON SURVIVAL OF INFLUENZA VIRUS

According to the author, a search for influenza virus in an institutional population during the fall, winter, and spring months revealed the presence of virus in the throats of symptomless persons 82 days preceding a clinically manifest epidemic and during the epidemic but not on other occasions. All but one strain isolated from influenza suspects in 1947 and 1948, as well as the strains isolated from the throats of symptomless persons shortly preceding and during the epidemic of 1947, are antigenically similar. They are also antigenically related to a strain (CAM) isolated in Australia in February, 1946.

While they may be regarded as belonging to type A influenza virus, they differ markedly from PR8 and A type virus isolated in 1943. There was no significant difference in the influenza attack rate among persons vaccinated with a commercial A and B type influenza vaccine four months preceding an institutional epidemic in 1947 than among those who were not vaccinated. Reference is made to a respiratory virus strain isolated in 1947 which appears to be antigenically unique.

(Taylor R. M. The Rockefeller Foundation New York, N. Y.: Studies on Survival of Influenza Virus Between Epidemic and Antigenic Variants of the Virus. American Journal of Public Health 30: 171-178 February, 1949.)

ESTROGENIC AND ANDROGENIC SMEARS AND FETAL SEX

Data is presented on a series of 89 pregnant women in whom vaginal smears were taken at various stages of pregnancy. Desquamated cells from the vaginal epithelium were obtained by insertion of a cotton applicator into the vault of the vagina. The staining procedure employed by these investigators was that of hematoxylin and carmine for the additional evaluation of glycogen. The normal vaginal smear changes during the course of pregnancy are presented.

Increased cornification without mucification was encountered in only six cases. Three of these soon thereafter threatened to abort. Specific estrogenic and androgenic smears are described and their significance and correlation to the fetal sex are discussed. The cytolytic smear consists of an increased number of Döderlein bacilli and complete destruction of cellular cytoplasm with intact nuclei and is believed to accompany high estrogen activity. This type of smear is associated with a female fetus. The mucoid cornified smear is the usual typical androgenic smear and is characterized by cornified cells with abundant mucoid material.

The glycolytic type, with extracellular glycogen and intracellular glycopenia, is a very rare androgenic smear. Such smears are associated with a male fetus. The extremely low incidence of specific smears during pregnancy limits the value of the vaginal smear method as a means for sex determination. The results, however, indicate that the maternal hormone levels change in accordance with the fetal sex. The source of the particular increased hormone is probably the fetus itself and the cases which either fail to show these specific changes or give errors may be explained by the fact that the maternal hormones may mask those of the fetus.

(Nieburgs, H. E. Augusta Ga. and Greenblatt Robert B. Specific Estrogenic and Androgenic Smears in Relation to the Fetal Sex during Pregnancy. American Journal of Obstetrics and Gynecology 57: 358-363 February, 1949.)

The Indian Physician

VOL VIII NO 9

SEPTEMBER 1949

WHOLE NO 93

Original Contributions

INTRACRANIAL TUBERCULOMATA*

by

A E DeSa, F.R.C.S. (Eng.)

K. L. M. Hospital and Jeebal Wadia Hospital for Children, BOMBAY

In spite of the frequency with which tuberculosis attacks the brain and its coverings tuberculomata constitute a small and declining percentage of all intracranial tumours, in the economically advanced and well nourished countries of Europe and North America

Van Wageningen in a study of 1,000 verified cases of intracranial tumours in Cushing's clinic (upto 1927) found 14 cases of intracranial tuberculomata—an incidence of 1.4%. None of these lesions was calcified. Cushing himself, in a subsequent analysis of 2,000 cases, placed the incidence at 2%. That this state of affairs did not always prevail in Europe is obvious from the writings of the older clinicians who estimated the incidence of tuberculomata at nearly 20% of all intracranial neoplasms. This decreased incidence must be correlated with improved health standards and the striking decrease of tuberculosis in general as compared with conditions that prevailed in Europe fifty years ago.

It is not surprising therefore that most of the current literature on intracranial tuberculoma comes out of the South American Republics where living conditions and health standards are demonstrably poorer than they are in the United States. It is the purpose of this paper to indicate that we have, in our country a fairly high incidence of intracranial tuberculomata which are missed or submerged in the clinical picture of tuberculous meningitis.

It is possible that the incidence of the disease in a highly industrialised city like Bombay, with its overcrowding, insanitary conditions, nutritional poverty and the possibility of tuberculous infection, is not a representative cross section of conditions in the country as a whole. In this regard, the autopsy findings of Garland and Armitage at Leeds are interesting. In a series of 13,000 autopsies, they found 89 cases of intracranial tuberculomata. Only two of these 89 cases, showed evidence of calcification.

Mode of Infection Intracranial tuberculosis is always secondary to an extracranial focus—which may be inactive or extinct. Three possible modes of spread have been postulated.

* A paper read at the 90th meeting of the Seth G. S. Medical College and K. L. M. Hospital Staff Society held on 12th March 1949, with Dr. A. V. Baliga in the chair.

(1) *by contiguity* as from tuberculous osteomyelitis of the skull or *primary tuberculous mastoiditis*

(2) *by perineural lymphatics* accompanying the cranial nerves from the nasal and pharyngeal cavities to the cranial meninges This view has never been adequately substantiated

(3) *by the blood stream* from a solitary focus in the lungs or mediastinal lymph nodes, or from generalised tuberculous foci

This view fits in with the accepted view of the origin of tuberculous meningitis The presence of tubercles of varying sizes in the brain, suggests a series of vascular "showers", and their presence in clusters around the branches of the middle cerebral artery lend colour to this conception It does not appear at autopsy upon these cases, that there has been a concentric spread from a primary focus, as when leptomeningitis follows surgical interference upon a gross tuberculoma This idea of vascular spread has been elaborated by Stefan Engel who in a critical microscopic study of the choroid plexus in tuberculous meningitis has shown how the villous process of the infected plexus expand into club shaped processes, shed their epithelium and finally fragment into and contaminate, the fluid pathways of the brain

PATHOLOGY

The pathological characteristics of tuberculosis in the brain are similar to those of tuberculosis in other organs, but it is worth remembering that the tuberculous granuloma is a product of the mesodermal tissues, the meninges, the vascular tree and the microglia The nervous tissue and the true neuroglia are destroyed by the advancing tuberculous lesion Tuberculomata are necrotising rather than expanding lesions, and hence signs of increased intracranial tension are often conspicuous by their absence, unless the lesion, by virtue of its location, interferes directly with the flow of cerebro spinal fluid

A great variety of tuberculous lesions of the brain have been described—both focal and diffuse, but the tuberculoma which is a focal tuberculous lesion consisting of masses of tuberculous granulation tissue, has to be distinguished from the true tuberculous brain abscess which resembles in most particulars, the common pyogenic abscess of the brain

It is an odd fact that true caseation is practically never found in brain tuberculomata There is invariably a solid centre even where the connective tissue response around the tuberculoma is negligible or absent In three of our series of seven cases that were autopsied, the centre was uniformly firm

It is possible that many tuberculomata of the brain escape detection at autopsy, because so many of them are asymptomatic during life, and the pathologist is reluctant to carry out a detailed examination of the brain at autopsy unless the clinical symptoms during life have pointed to the brain as the probable seat of the disease, and because so many tuberculomata may elude any but the most painstaking search

Lewison, Freilich and Ragins found 20 cases of tuberculoma of the brain in the autopsy material of the Cook County Hospital, 11 of which had not even been suspected during life, only 2 of these 20 cases had given rise to symptoms suggestive of an intracranial lesion Garland

and Armitage are of the opinion that 75% of intracranial tuberculomata are silent till meningitis supervenes

Location —Intra encephalic tuberculomas have a predilection for the cerebral and cerebellar cortex, though they may be found in any and every part of the brain

Scott and Graves in a study of 815 proven cases of intracranial tuberculomata showed that they occur as frequently in the posterior cranial fossa as in the entire supratentorial region, and that they lie in contact with the surface of the cerebral convexities in a bare 20% of cases. In two-thirds of the total number of cases, but a single tuberculoma was found

An interesting development in the life history of an intracranial tuberculoma from the diagnostic and prognostic points of view, is the occurrence of calcification. Calcification in a tuberculoma implies a high degree of tissue resistance and a more or less successful effort on the part of the body to heal the tuberculoma. Such lesions are necessarily of great chronicity and calcified tuberculomata have been known to exist for periods varying from four to sixty years. Calcification is a rare development in intracranial tuberculoma. Scott and Graves in the series already mentioned, found only 11 instances of calcification (1.3%). Weinberger and Grant in stressing the infrequency of the condition, state that only 19 verified cases of calcification in intracranial tuberculomata, had been reported till the end of 1942. Evans and Courville found evidence of calcification in 3 out of the 43 cases of brain tuberculoma that they studied (6.6%). Pancoast and co authors found no verified cases of calcified intracranial tuberculoma in the material of the University of Pennsylvania. They believe that the lack of routine x-rays of the skull of tuberculous patient does not permit of a true estimate of their incidence

Chart showing Incidence of Calcification in intracranial Tuberculoma

	No. of cases of intracranial Tuberculoma	Calcification found in	Percentage
Van Wagenen (Cushing's series)	14	nil	nil
Garland and Armitage	89	2	2.51
Scott and Graves	815	11	1.3
Evans and Courville	43	3	6.6
Pancoast et al	No calcified intracranial tuberculoma in the material of the University of Pennsylvania		
Weinberger & Grant	19 verified cases in all the literature		
Present series	7	2	

The two instances of calcification in our series of seven cases are an indication of the high tissue resistance to tuberculosis that Indian children display, and have an indirect bearing upon the line of treatment that, in my opinion should be adopted in these cases

Calcification, must not be too readily accepted as conclusive evidence of healing of the tuberculoma, because cases of fatal tuberculous meningitis have been described as supervening upon calcified tuberculomata. Other causes of death in calcified tuberculomata are internal hydrocephalus, Addison's disease and pulmonary tuberculosis

Broadly speaking, the quiescence of calcified tuberculomas is exemplified by the long survival of some of these cases (over 60 years in one authentic case), and of the eighteen cases collected by Evans and Courville six were alive for periods varying from $7\frac{1}{2}$ to 11 years after the diagnosis had been established

Calcified tuberculomata are commonly formed in the cerebral hemispheres. Because of the multiple in-foldings of the pia in the cerebellar folia, there is closer contact between cerebellar tuberculomata and the leptomeninges. Tuberculous meningitis is consequently an early and lethal complication in tuberculomata of the cerebellum and calcification of the tuberculoma is more or less effectively precluded

Symptomatology —From the point of view of symptoms, these cases fall naturally into two broad groups, those in which the tuberculomas are small, multiple and diffuse and where the symptoms are those of tuberculous meningitis, and those in which there are one or two tuberculomas and the symptoms are localising in character like those of a brain tumour, or merely indicative of increased intracranial tension

In the first group of cases, the presence of the tuberculomas may never be suspected, because tuberculous meningitis can produce focal signs by invasion of the brain substance

A critical study of the factors determining which of these two syndromes will develop in any given case has been undertaken by Jaffe and Schultz in an examination of the extracranial tuberculous foci associated with tuberculomas of the brain. Their conclusions which have been confirmed by the findings of Buchstein and Adson are that tuberculomas producing symptoms of cerebral tumour occur at all ages and in persons who have but a single extracranial focus in the lungs or associated lymph nodes. On the other hand, tuberculomas that are associated with the clinical picture of meningitis occur predominantly in the younger age groups and as part of generalised tuberculosis

With the calcified intracranial tuberculomata, however, extracranial foci of tuberculosis are not invariably present. In this connection the report of Garland and Armitage previously referred to, in which an extracranial tuberculous focus was found in every one of the 89 cases of intracranial tuberculoma studied, is revealing

The symptoms may be divided into focal, local and constitutional. The focal symptoms depend upon the anatomical location of the disease. As the cortical portion of the hemispheres is usually involved, convulsions, seizures, paresis or paralysis on the contralateral side often occur. J. Purdon Martin has described fits which resembled "petit mal". Four of our series of cases gave a history of "fits" which varied from simple twitchings of an extremity to clonic convulsions involving one half of the whole body. If the sensory cortex is involved, loss of sensation and astereognosis may occur, this happened in one of the cases detailed below. With cerebellar tuberculomata, the cerebellar signs predominate. As we were dealing in our series with quite small children (average age $3\frac{1}{4}$ years), it was not always possible to say with certainty whether cerebellar signs were present or not. In one case in this series, cencephalography was followed by a convulsive seizure, and the patient remained in a position of opisthotonos for over five minutes, confirming the radiological diagnosis of a tumour of the vermis of the cerebellum

Though the local symptoms of increased intracranial tension, headache and vomiting, are believed to be of late and infrequent occurrence, four of our series of cases came in for headache as the principal symptom, and three for what appeared to be causeless vomiting. Among the presenting symptoms in the seven cases here considered were

Paralysis	4 cases
Fits	2 cases (one after encephalogram)
Ataxia	1 case
Papilloedema	2 cases
Pallor of temporal half of optic disc	1 case

Pyrexia was a feature of every case at some time or other in the course of the illness

Two cases not included in this series were admitted with a diagnosis of "cerebral tumour" and while under observation in the wards, developed the full-blown picture of tuberculous meningitis

Extracranial Tuberculous Foci —Being aware of the great frequency of intracranial tuberculomata in children, we have made it a point to X-Ray the lungs in every case suspected of an intracranial tumour. Of the seven cases, one child had bilateral infiltration of the lungs, bilateral tuberculous cervical nodes (proved by biopsy) and tuberculous nodes in the abdomen

Another child in this series had cutaneous tuberculosis, tuberculous axillary nodes, tuberculous arthritis of the elbow and tuberculous osteomyelitis of the skull

Accessory Examinations —So important is an accurate etiological diagnosis as between intracranial tuberculoma and intracranial tumour from the point of view of prognosis as well as treatment, and so notorious is its infrequency, that we have cast about for some biochemical test on which an unequivocal diagnosis of intracranial tuberculoma could squarely rest. We have noted exacerbations in the natural history of intracranial tuberculomata, which coincide with a clinical picture of neck rigidity, headache and temperature. These phases probably represent a temporary contamination of the fluid pathways of the brain by a spillage of tuberculous material

Repeated examinations of the cerebro spinal fluid in some of these cases (proteins, chlorides, cells, tubercle bacilli) in the hope that we might have the good fortune to "catch the lesion" during one of these spillages have not been rewarded

We have not noted any significant alteration in the cellular or chemical composition of the cerebro spinal fluid of our cases

Examination of the fundus oculi for the presence of choroidal tubercles is an important link in the chain of diagnosis, concerning the nature of a space occupying lesion in the brain. One of our colleagues at B J Hospital for Children has been able to demonstrate to our satisfaction the presence of choroidal tubercles in two cases where diagnosis lay between an intracranial tumour and intracranial tuberculoma. In this connection, one must stress the importance of a prolonged and of painstaking search by a competent fundoscopist. Recent authorities have

gone so far as to say that a minimum of half an hour's examination is necessary before the presence of choroidal tubercles can be ruled out

Diagnosis —In spite of careful general examination and the marshalling of all necessary laboratory and ophthalmoscopic aids, it is unusual for a correct diagnosis to be made before operation or autopsy

In twelve of Garland and Armitage's cases, a diagnosis of brain-tumour was made and in only one case, was a tuberculoma as much as suspected

Dandy believed that the basis for the diagnosis of an intracranial tuberculoma is the presence of tuberculosis elsewhere in the body. The presence of tuberculous lymphadenitis, pulmonary tuberculosis or tuberculous peritonitis, might furnish important clues to the correct diagnosis

Röntgenograms —There are no pathognomonic signs of intracranial tuberculoma, though the consequences of a space occupying intracranial lesion may be manifested by the usual signs of raised intracranial tension (open fontanelles, wide sutures, silver-beaten appearance, erosion of clinoid processes)

If calcification occurs, the typical appearance is an irregular, broken calcareous shell. The calcified shadows may be multiple, lobulated and irregular. These irregularities can be explained only by periodic recrudescence of activity in the tuberculoma, with local extension of the disease process

The margins of a calcified tuberculoma are usually sharply defined and the edges serrated. The densest portion of the calcified mass is usually at the periphery. Since the cortex is the site of choice for most tuberculomata these calcified shadows are commonly seen near the inner table of the skull. But as the distribution of cortical substance extends over the mesial aspect of the hemispheres and the base of the brain, the shadows may make their appearance at a great distance from the inner table of the skull

In brief it must be borne in mind that these radiological data are not diagnostic, and that the identity of the shadows must be finally established by correlation with clinical data

Cerebral Pneumography —This procedure has the same value as it has in cerebral tumour—as indicating any deformation or non-filling of the ventricular system

I have noticed that the cortical subarachnoid space fails to fill with air in the neighbourhood of a tuberculous granuloma. I suggest that this might serve as a valuable distinguishing point between a cerebral tumour and cerebral tuberculoma. For whereas intracranial tuberculomas tend to cortical localisation and can by their nature infiltrate into the subarachnoid space, neither this localisation nor behaviour is typical of the common supratentorial tumours. The only tumour that is known to invade and infiltrate the meninges is the medulloblastoma, but as its localisation is the posterior cranial fossa, and its natural history is brief and lethal, diagnostic confusion is unlikely to arise

A brief resume of the seven cases here analysed is presented

Name	Presenting Symptoms	Site	Confirmation By
1 RANI (Fig I)	Headache loss of power Intention tremors	Parietal	Operation & Ray (Calcification)
2 SITARAM	Headache, vomiting	Temporo-Sphenoidal	Post mortem
3 MANDAKINI (Fig II)	Headache vomiting ataxia	Vermis of Cerebellum	Post mortem
4 VIJAYA	Fits hemiplegia T B ulna hilar glands enlarged, cutn neous tuberculosis	Parietal	Collateral clinical evidence
5 NAINI	Hemiplegia hydrocephalus tuberculous hilar nodes and cervical nodes	Cerebellar	Collateral clinical evidence
6 CHANDRAKANT (Figs III V)	Fits Hemiparesis	Peduncular	X Ray (Calcification) Accessory Evidence
7 MANDAKINI	Headache vomiting	Cerebellar	Operation

Case 4—is still alive—1 year after diagnosis of the intracranial condition The hemiplegia is recovering under intensive physical therapy and massage

Case 6—has been lost trace of, though he was followed up for three months

Case 7—died of tuberculous meningitis one year after cerebellar decompression

TREATMENT

There has been a recent revival of interest in intracranial tuberculomas as a neuro surgical problem from the success that has attended radical surgery in selected cases

Briefly expressed the treatment may be conservative or operative Operation may be radical or undertaken merely as a palliative measure The first attempt at radical extirpation of an intracranial tuberculoma was undertaken by Hahn in 1880, three years before Rickman Godlee's well-known operation

There has been a sharp cleavage of opinion with regard to the place of surgery in the treatment of these lesions Cushing was in favour of simple decompression supplemented by general measures—especially for cerebellar tuberculomata, which constituted the majority of his lesions

Dandy, on the other hand, roundly condemns decompression as a valueless operation and advocates wide excision of solitary tuberculomata

Parker, commenting on the problem of intracranial tuberculomata in Ireland, states that simple decompression often results in amelioration of symptoms

It is argued against attempts at surgical extirpation, that the lesions are often multiple and lie in inaccessible regions, that extirpation of the intracranial tuberculoma does not eliminate extracranial foci which may

* *Case 4*—Since writing this paper this child has recovered power in both the left lower and upper extremity except for slight residual weakness in the left hand From being bed ridden she is on her feet again

Apart from receiving 20 grammes of Streptomycin she has been put through a course of muscle re-education and physiotherapy

The near completeness of her recovery throws an interesting sidelight on the tremendous regenerative powers of childhood

cause death or lead to further tuberculomata in the brain. The risk of fatal post-operative meningitis is stressed, and as healing does not occur in these tuberculomata, it is argued that general anti-tuberculous measures should be tried.

The advocates of radical surgery point out that operation is commonly undertaken for solitary tuberculoma, that successful operations have been undertaken even in the presence of active pulmonary tuberculosis and that what appears to be a tuberculoma, may prove, as in two Cushing's cases, to be a benign type of neoplasm, (Ependymoma, Xanthoma).

Finally, though the patient may eventually die of tuberculosis, a period of welcome relief may be obtained.

The consensus of opinion would appear to be that cerebellar tuberculomata are unsuitable for radical surgery, from the technical difficulties of total ablation and the ever present hazard of tuberculous meningitis.

Buchstein and Adson record two radical extirpations of cerebellar tuberculomata, apparently successful, which ended in the death of the patients over a month later. An outstanding example is Frazier's successful case, quoted by Kwan, in which the patient was alive and well, eleven years after operation.

The group of tuberculomata adjacent to the cerebral cortex offer the brightest prospects to surgical excision. Not only are they surgically accessible, but from their usual position close on the central sulcus, their early recognition is more or less assured.

Buchstein and Adson collected reports of 21 cases of complete excision of cerebral tuberculomata in the decade 1930-40. There was one operative death, and six others died at intervals varying from eleven to twenty four months, of intracranial or pulmonary tuberculosis. The rest were reported as being alive for periods of time extending upto nine years.

Excision of calcified tuberculomata does not involve the same risk of tuberculous meningitis as does excision of the uncalcified tuberculoma. Surgical literature before 1930 records a number of successful extirpations of calcified tuberculomata. These tuberculomata being quiescent or healed, however, are precisely those in which surgery is not imperative.

The great surgical blunder in the operative management of intracranial tuberculomata is the performance of a biopsy or partial removal. Such a procedure is bound to end in the development of tuberculous meningitis. The occasional successes from radical surgery must not be allowed to prejudice one's judgement with regard to treatment, and one must remember the natural tendency of most writers to report only their successes.

It is my opinion that Indian children have a high natural resistance to intracranial tuberculoma (the high incidence of radiological calcification in our series, would appear to confirm this opinion) and that misguided and meddlesome attempts at radical extirpation, may only terminate in dissemination and death. It must be remembered that the best results in operations of this magnitude are only obtained by neuro-

surgical teams, and by a refinement of neuro surgical technique which we have still to attain

In the light of my experience, I would restrict surgery in the unequivocally proven case, to palliative decompression in order to circumvent blindness or relieve headache. I would depend on general anti-tuberculous measures and the problematic effects of streptomycin, to bring about healing.

I say problematic because recent trends indicate that though Streptomycin is of supreme value in the treatment of tuberculous meningitis, there is only a minimal excretion of the antibiotic into the brain tissue, which precludes its effective action on brain tuberculomata.

SUMMARY AND CONCLUSIONS

(1) The frequency of intracranial tuberculoma in the younger age group is stressed—seven cases in three years (1946-1948)

(2) It is necessary to suspect the lesion, if an accurate diagnosis is to be arrived at—in a case, where the signs and symptoms point to an expanding or space occupying intracranial lesion.

In such a case an assiduous search must be made for extracranial foci of tuberculosis and the lungs x-rayed as a routine.

(3) Painstaking fundoscopic examination for the presence of choroidal tubercles can be of great value in confirming the diagnosis.

(4) It is suggested that repeated examinations of the cerebro-spinal fluid might, at some stage in the evolution of the disease, throw light on the diagnosis of the condition.

(5) A critical examination of the plain radiograph for evidence of calcification should be made.

(6) The high incidence of calcification (two out of seven cases) in this series is stressed and the conclusion drawn that the tendency to spontaneous healing is strong.

(7) If the diagnosis is unequivocally established, general anti-tuberculous measures, with or without a palliative decompression, is the treatment of choice.

REFERENCES

1. BUCHSTEIN, H. F. and ADSON, A. W. Tuberculoma of the brain. *Arch Neurol and Psychiat* 1940, 43: 635-648.
2. CUSHING, H. Intracranial Tumours. Notes upon a series of 2 000 verified cases with surgical mortality percentages pertaining thereto. Springfield Ill: Charles C. Thomas 1932.
3. DOTT, NORMAN and LEVIN, ERNEST. Intracranial Tuberculoma. *Ed Med Journal* 46: 36-41 (Jan-June) 1939.
4. ENGEL, STEFAN. Pathogenesis and Clinical symptoms of tuberculous meningitis. *The British Journal of Children's Diseases* 34: 38 (April-June) 1944.
5. EVANS, H. S. & COURVILLE, C. B. Calcification and Ossification in Tuberculoma of the Brain. *Arch Surg* 36: 637-659: (April) 1938.
6. GARLAND, H. G. & ARMITAGE, G. Intracranial Tuberculoma. *J Path and Bact* 37: 461-471 (Nov.) 1933.
7. JAFFE, R. H. & SCHULT, H. The relation between Tuberculomata of the central Nervous system and tuberculous changes in other organs. *Am Rev Tubec* 33: 302-312 (March) 1936.
8. KWAN, S. T. Tuberculoma of the brain with a report of a case eleven years after operation. *Arch Neurol and Psychiat* 22: 1093-1094 (Nov.) 1929.
9. LEWISON, M., FREILICH, E. D. and HAGINS, O. B. Tuberculoma of the brain. *Ann Int Med* 7: 1141-1145 (March) 1934.
10. MARTIN, J. PURDON. Calcified intracranial tuberculomata. *British Journal of Radiology* Vol No 109: 5-18 (Jan.) 1937.
11. PANCOAST, H. K., PENDERGRASS, E. P. & SCHAEFFER, J. PARSONS. The Head and Neck in Roentgen Diagnosis. Springfield Ill: Charles C. Thomas 643 1910.

- 12 PARKER H L Disease of the nervous system in Ireland Some observations and comparisons Proc Staff Meet Mayo clinic 12 402 403 (Aug 4) 1937
- 18 SCOTT, E and GRAVES G O Tuberculoma of the brain with a report of four cases *Am Rev Tuberc* 27 171 192 (Feb) 1933
- 14 VAN WAGENEN, W P Tuberculoma of the brain Its incidence among Intracranial tumours and its surgical aspects *Arch Neurol and Psychiat* 17 87 91 (Jan) 1937
- 15 WEINBERGER LAWRENCE M and GRANT FRANCIS C Calcified tuberculoma of the brain *Am Jour Roent* 47 525 533 (Jan June) 1942

NICOTINIC ACID METABOLISM*

Dr R G Chitre, M Sc, Ph D, read a paper on "Some aspects of Nicotinic Acid Metabolism" He reviewed briefly the literature on the various nicotinic acid compounds which are important from the point of view of physiology of that vitamin He also stated that the total amount of an essential nutrient in the food-stuff is not the same as that which is physiologically assimilable It is worth-while remembering this difference between total and available content of an essential nutrient in a foodstuff to understand the metabolism of vitamins in particular

The chemical and microbiological methods of estimation of nicotinic acid give only approximate idea about the potency of a particular food The amount of nicotinic acid available for nutrition may not always be identical with such estimations Suitable experiments (biological) were carried out on rats as regards, (1) the excretion of nicotinic acid on standard diets, and (2) the absorption of the acid from the intestine

The first type of experiments gave a qualitative indication as to the difference between the total and available content of nicotinic acid while the latter showed the quantitative difference

On the basis of these findings a method of Enzymic hydrolysis of food-stuffs *in-vitro* was developed by Dr R G Chitre which gave figures for the nicotinic acid comparable and statistically not different from the physiologically available nicotinic acid *in-vivo*

* Summary of Dr R G Chitre's paper read at the 92nd meeting of the Seth G S Medical College and K E M Hospital Staff Society held on Saturday the 14th May 1949

PLATE I

DeSa—Intracranial Tuberculomata

THE INDIAN PHYSICIAN—Sept 1949

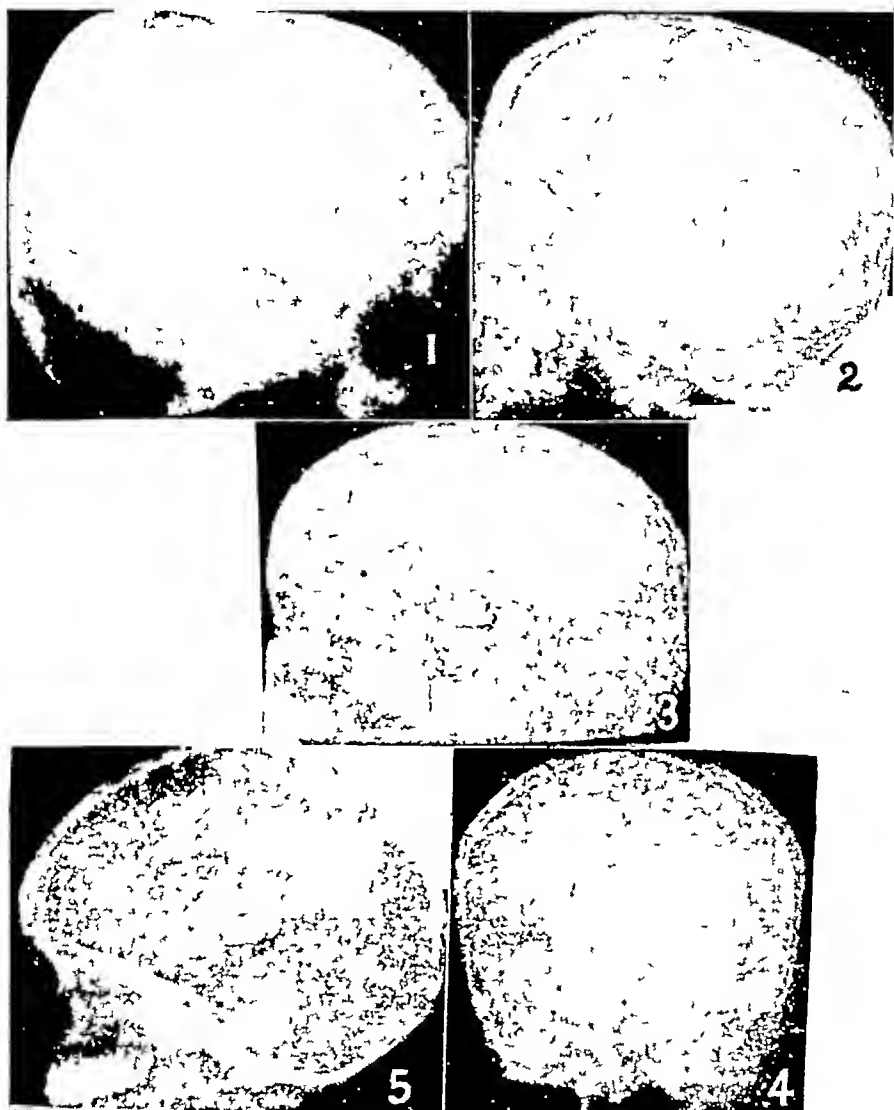


Fig 1 Encephalogram Non filling of the body of the lateral ventricle and failure of the cortical subarachnoid space to outline with air The significance of this sign has been referred to in the text Calcification faintly visible

Fig 2 Ventriculogram Filling defect in the fourth ventricle which is clearly outlined

Fig 3 Roentgenogram Calcification in the tuberculoma

Fig 4 Roentgenogram Calcification some distance away from the mid line

Fig 5 Encephalogram Calcification outside the ventricular system

PLATE II

Patkar—Row's Medium for *Leishmania*

THE INDIAN PHYSICIAN—Sept 1949

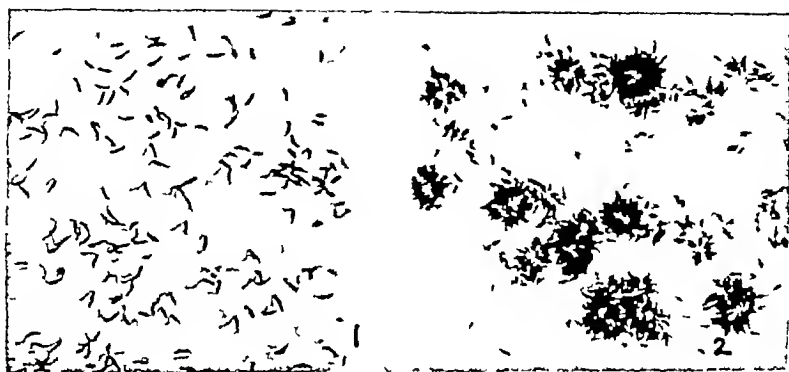


Fig 1—*Leishmania tropica* Cambay on solidified haemoglobin blood agar 29 7 30/8 8 36

Fig 2—*Leishmania tropica* Cambay grown in Row medium (Haemoglobinised Saline) 8 8 30/0-11 36 illustrating the longevity of parasite

Fig 3—*Leishmania tropica* Cambay 12 days culture in Row medium

Fig 4—*Leishmania tropica* Cambay 12 days culture in Row medium turning slowly into methaemoglobin

Fig 5—*Leishmania tropica* Cambay over four weeks culture in Row medium changing mostly into methaemoglobin

Figs 3 4 & 5 illustrate reversion of *Leptomonads* into *Leishmanoids* in culture

VALUE OF ROW'S MEDIUM FOR CULTURE OF LEISHMANIA IN KALA-AZAR

A REVIEW

by

N A PATKAR, M BBS

Dept of Pathology P G Shingane Hindu Hospital BOMBAY

Before establishing a definite diagnosis of Kala azar it is essential to confirm the clinical findings in suspected cases, by pathological investigation of the available biopsy material such as, that from Hepatic or Splenic puncture, bone-marrow and even of peripheral blood. The most important point in these studies is to ascertain microscopically, the presence or absence of Leishman-donovan bodies—all other observations being only of secondary value. These refer to blood changes viz, haemoglobin content, total and differential blood cell count or alterations in blood serum e.g. Napier's formal gel reaction, Urea stibamine test or increase of euglobulin. Once the Leishman donovan bodies are detected definitely, it is hardly necessary to go any further. It is only when these parasites are absent or not definitely recognised that one has to proceed to culture the suspected material in a suitable culture medium. In the early days, Citrated Normal Saline was found quite satisfactory for obtaining the first culture and a few subcultures of the Leishman donovan bodies. L Rogers¹ & ² to whom belongs the credit of the discovery of the development of the Leishman donovan bodies from the splenic blood into Leptomonads—flagellates made use of this simple salt solution for his culture medium in Calcutta. Row also made use of the same nutrient medium in Bombay in his first demonstration of the same phenomenon for the Leishmania tropica of the Oriental sore of Cambay and also in his study of the development stages of the parasites before they finally assumed the Leptomonad forms (flagellates). But both these observers and those who followed, found that the simple citrated normal saline though satisfactory for the first cultures, failed when used for maintaining serial subcultures and the problem of having a more suitable nutrient medium remained unsolved till Nicolle demonstrated that the condensation fluid of the rabbit blood agar slopes, which Novy-McNeil³ & ⁴ had found useful in the study of cultures and serial subcultures of Trypanosoma Lewisii and of Nagana, eminently suited for the culture and subculture of Leishman donovan bodies also. This N N medium was simplified by Nicolle,⁵ & ⁶ by eliminating the peptone and meat extract from the nutrient agar with which Novy and MacNeil had incorporated at 55°C with twice the quantity of defibrinated rabbit blood to allow for the accumulation of satisfactory quantity of the condensation fluid and this has been the nutrient fluid invariably used by all workers on Leishmania and is the well known N N N medium. Row also utilised it in his earlier experiments but found its preparation too laborious and complicated and also too expensive as it required a large quantity of rabbit's blood at each time of the preparation and therefore he devised in 1912 the Haemoglobinised saline (Row) medium⁷ & ⁸. It is simple and very economical and easily

prepared in a few minutes all that is required being a few drops of defibrinated rabbit's blood, a little sterile distilled water and sodium chloride solution of double the normal strength. The chief value of the nutrient becomes impressive when one has to culture the peripheral blood in suspected cases where the parasites are either absent or not definitely demonstrable. In all such cases Row has made use of a few drops of peripheral blood taken up in citrated saline for the infecting material even when this reached his laboratory some times after 4 or 5 days delay in transit.

The report on the blood examined by culture of the two cases at the Singhanee Hospital given in the appendix, may be found interesting and illustrative of the value of the Row's medium as the blood of one of them (case No. 1) examined was cultured for curiosity because there was the least suspicion of kala-azar, the patient being a resident of a "Dry Area" where Kala azar has not been known to occur endemically and whose bone marrow had failed to reveal the Leishman donovan bodies, although the blood serum changes were well marked, the other (case No. II) whose blood was tested by culture, was resident of also a "Dry Area" for Kala azar but where Oriental Sore has been known to occur in the neighbourhood his blood and bone marrow also showed no parasites and even splenic blood smear no definite result.

Since 1912, Row has used his haemoglobin saline solution as a routine and invariably for the peripheral blood examination by culture on which he always depends, as he has not had a single failure in all the cases of suspected Kala-azar. He has also made use of the same culture fluid in all his studies connected with Leishmania and other flagellates as some of the observations quoted in the references may show, they include (i) Preparation of solidified Haemoglobin Saline for surface culture of Leishmania,¹² (ii) Observation on the longevity of Leishmania tropica in culture *Vide*, Figs 1 & 2 plate 1,¹³ (iii) Study of Leptomonas davidi (plant leptomonads) in culture,⁹ (iv) Technique of culture of Kala-azar from finger blood,¹⁰ (v) Reversion of Leptomonads to Leishmanoids in culture¹¹ (vi) Role of Methaemoglobin on this Reversion from Leptomonads to Leishmanoids,¹⁴ (*Vide* Figs 3, 4 & 5 Plate 1) (vii) In this medium the strain has been maintained since 1912 in subcultures.

In brief, here is a culture medium simple in composition and easy, rapid and economic in preparation for immediate use and it is to be hoped that this culture medium will be better recognised and more universally applied in the study of leishmaniasis.

APPENDIX

Case 1—S S, 12, female, Residence Bombay and Sholapur (for four months at Sholapur)—(Both "Dry Areas" for Kala-azar—second indigenous case reported at P G Singhanee Hospital, Bombay)

Complaint—Low fever daily for four months, 'Pot-belly' one month, Weakness and loss of weight 2 months

State on admission—(26-11-48) Pale and weak, abdominal swelling, liver not palpable, spleen enormously enlarged reaching almost to the Symphysis pubis, Nothing abnormal in other systems

Blood Examination—(26-11-48) Venous blood, Haemoglobin 50.0%, R B C 2,000,000/cmm, W B C 1950/cmm, Diff count,

Polymorphs 60 0%, Lymphocytes 32 0%, Monocytes 3 0%, Eosinophils, 5 0%, Parasites Nil

Blood serum —Napier's Formol gel reaction Positive, Euglobulin increased

Venous blood culture (26-11-48) Leptomonad forms detected in large number (Culture grown in Row's medium), 15 days culture at 24°C (11-12-48)

Sternal puncture —Parasites not definite

Treatment started on 27-11-48 and discharged cured on 16-12-48

Results on discharge Patient improved in general health, increase in weight by 5 pounds, Anaemia less marked, Spleen greatly reduced in size and was just palpable below the costal margin

Blood examination —Haemoglobin 72 0% R B C 3,320,000/cmm, W B C 5,150/cmm, Diff count Polymorphs 62 0% Lymphocytes 28 0%, Monocytes 6 0%, Eosinophils 4 0%, Parasites nil, Serum Napier's Formol gel reaction Negative Blood culture in Row's medium negative 4 weeks

Case II —K D, 35, male, sweeper Residence Bhavnagar Kathiawar and Bombay since last two years (Both "Dry Areas" to Kala-azar but the former reported for endemic Oriental sore in the neighbourhood)

Complaints State on admission into Singhanee Hospital (4-7-49) Irregular low fever for 7-8 days daily off and on for last two years, loss of appetite, swelling in the abdomen, weakness, frequency of stools with blood and mucous for 14-15 days

Clinical findings —Temp 99°F Pulse 100/min Resp 20/min Not particularly pale but weak, liver just palpable, spleen enlarged midway between Umbilicus and Symphysis pubis, no abnormality in other systems

Blood examination —Haemoglobin 72 0%, R B C 3,800,000/cmm W B C 4,100/cmm, Diff count Polymorphs 72 0% Lymphocytes 20 0%, Monocytes 5 0%, Eosinophils 3 0%, Parasites nil

Blood serum Napier's Formol gel reaction Positive, Euglobulin increased

Venous blood culture —In Row's medium (7-7-49) Positive for Leptomonads (flagellates) detected on 21-7-49 (14 days at 24°C) Parasites fat and short more alike to *Leishmania tropica*

Spleen puncture —(18-7-49) Leishman donovan bodies ill-defined, Culture in Row's medium grown Leptomonad forms (flagellates on 25-7-49, parasites fat and long

The Department of Pathology, Singhanee Hospital reported on 28-7-49 that the culture from the peripheral blood strongly suggests this case may be generalised infection by *Leishmania tropica*, both by the vigour and rapidity of development and morphological characters of the parasite

Technique for preparing Row's medium for immediate use —A few c.c.s of rabbit's blood either from heart or from marginal vein in the ear, defibrinated, are added to 8-10 times the quantity of sterile distilled

water and after 2—3 minutes of vigorous shaking, is distributed in tubes for centrifuging and separating the clear haemoglobin solution from the deposit of the dehaemoglobinised stroma and Leucocytes, this is mixed with an equal quantity of sterile normal saline of double strength and distributed in small sterile test tubes, 5 ccs of rabbit's blood yield over 20 culture tubes of Row's medium each for immediate use, a trace glucose (one drop of 25% solution in water per 5 c c of the medium improves the keeping qualities of the culture fluid. The whole process does not take more than 20 minutes

I am very grateful to Dr R Row M D (Lond), D Sc (Lond) for supplying me with the material and advice in preparing this brief review

REFERENCES

- 1 L ROGERS Flagellates from Leishman Donovan Bodies in Culture *The Lancet* 1904
- 2 IDEM Flagellates from Leishman Donovan Bodies in Culture *Proc R Soc* Feb 1905
- 3 NOVY & MACNEIL Culture Fluid for Trypanomes Nagana & N N Medium *Jour of Im Med* 1ss Nov 1903
- 4 IDEM Culture Fluid for Trypanomes Nagana & N N Medium *Jour Inf Diseases* Jan 1904
- 5 NICOLLE Culture of Leishmania in Mediterranean Kala azar & of Oriental Sore of Biskra in Simplified N N Medium now known as N N N Medium *Bull Soc de Path Exot Tunis* April 1908
- 6 IDEM & MANCEAUX Culture of Leishmania in Mediterranean Kala azar & of Oriental Sore of Biskra in simplified N N Medium now known as N N N Medium *Bull Soc Path Exot Paris* April 1911
- 7 R ROW Development of Flagellated Organism from the Parasite of Oriental Sore of Cambay *Proc Bom Med Cong* Feb 1909
- 8 IDEM A Simple Haemoglobinised Saline Solution for growth of Leishmania *Quat JI After Sc* July 1909 *Br Med Jour* 1912
- 9 IDEM Culture of Leptomonas Davidi (plant flagellate) from Lurhorbia Philipherna *Tr Gr Co Med Soc* 1915
- 10 IDEM Technique of culture of Leishmania from I nger Blood in Kala azar *Ibidem* 1917
- 11 IDEM On Reversion of Leptomonads to Leishmanoids in Culture of Kala azar Blood *Ind Jour Med Res* 1923
- 12 IDEM Simple Solidified Haemoglobinised Saline for surface Culture of Leishmania *Ind Med Gaz* 1939
- 13 IDEM On Longevity of Leishmania Tropica in Culture in Row's Medium April 1935 *Bull Soc Path Exot Paris*
- 14 IDEM & KULKARNI Role of Methaemoglobin in Row's medium in the Reversion of Leptomonads into Leishmanoids in Culture *Ind Med Gaz* 1943

Reflections and Aphorisms

LAMENTING THE PRACTITIONER "Having nothing to do, they took to healing. What do such people know about the value of human life? Or that saving is not a business proposition? They only read half a medical book and learn the use of a few drugs. Before starting practice they ask what medicines the popular quacks are using and then try them on their patients. If some good results follow, they are themselves amazed, if death occurs, they insist that the medicine was good but that the disease was fatal. How many innocent boys and girls, young husbands and wives, aged fathers and mothers have been killed? And people do not blame you but, on the contrary, compensate you for attendance and medicine! Oh, how could you have the heart to do it? Though the law cannot reach you, yet heaven will not be deceived. Should you really want to serve suffering humanity you must first read more. If unable to do so, better change your profession so as to escape the fires of hell."

HSU LING T'AI (CH'YEN LUNG PERIOD—A D 1780-1790)

ANTIHISTAMINE DRUGS IN DERMATOLOGY

by

J A FERNANDEZ M R C P (Ld),

M R C S (Eng) L R C P (Lond)

Hon Dermatologist & Venereologist R E M Hospital Parel BOMBAY

and

M S TRASI, M B B S

(Late Capt I A M C)

Histamine is a base of the formula β -imin-azoly ethylamine. Its pharmacological actions are, a fall of B P due to a dilator action on the arteries and an increase in the capillary permeability. None of the fall is of cardiac origin for, histamine stimulates the heart. A prick through a drop of histamine placed on the forearm produces a red flare first due to a dilator action on the capillaries, and a wheal later, due to leakage of fluid out of them. Another action of histamine is a contraction of plain muscle, a striking effect being contraction of the bronchioles with resulting dyspnoea. It also increases intestinal movements. But on the coronary arteries it has a dilator action. In lethal doses it kills animals by contraction of the plain muscle, the form of death varying in different species according to the difference in the distribution of the plain muscle attacked. Thus guinea-pigs are killed by bronchial contraction, dogs by accumulation of blood due to contraction of the collecting venules of the hepatic veins, and rabbits from pulmonary arterial contraction.

Anaphylaxis —This is an acquired sensitiveness where allergy is inherited and often occurs in the members of the same family. Anaphylaxis is caused necessarily by a protein matter to which one must have had a previous exposure. In the latter it need not be a protein. It has been found that an injection of egg albumin into a guinea pig 8—4 weeks after a preceding similar injection causes an anaphylactic shock due to sensitization, the animal dying due to bronchial contraction in the same way as it would if given a lethal dose of histamine. These similarities and experimental evidence of Dale and Best proved that histamine was a normal constituent of all tissue cells and led to the view that anaphylaxis in animals was probably due to histamine liberation from the tissue cells. It is probable that the tissue cells are normally insensitive to its presence but when histamine is liberated by trauma, infections, toxins, antibody-antigen union, it produces its specific local or constitutional disturbances by acting on responsive cells in the bronchioles, blood vessels, gut, etc.

Although the reactions induced in experimental animals are stereotyped and spontaneous reactions in man have a varied pattern, it required no stretch of imagination to assume anaphylaxis and allergy are similar and that histamine release occurs in the latter also and is casually related to some of the phenomena of these reactions. Although it is not the sole factor concerned it is enough to warrant therapeutic measures suggested by such an assumption. There is evidence that the effects of histamine are qualitatively consistent with certain allergic phenomena as may be produced by certain foods in a sensitive person, or by a drug, Quinine or aspirin, to which some are sensitive.

Allergy — There are two forms of allergy Atopic and Non-atopic. Atopic allergy is said to have the following characteristics —

- (a) Symptoms explicable by increased capillary permeability and smooth muscle spasm
- (b) Family and personal history often includes asthma or hay-fever, atopic dermatitis
- (c) Eosinophilia in smears of transudates and other secretions
- (d) Circulating antibodies found which are transferable (Prausnitz-Kustner bodies)
- (e) Scratch or intracutaneous test gives a wheal and a flare response
- (f) Allergens are antigens and may be pollens and other plant or animal emanations, insects, spores, dust, fur clothing, cosmetics, sera, vaccines, parasites, drugs and other substitutes

Non-atopic allergy —

- (a) Occurs in any one after adequate exposure
- (b) Manifests itself after a time interval, following the sensitizing contact with or without subsequent exposures
- (c) Lesions caused by unknown mechanism are epidermal eczematous, with papules, vesicles and microscopically, spongiosis
- (d) No wheal reaction, no circulating transferable Prausnitz-Kustner bodies No family history of atopy
- (e) Cause can be identified by eczematous reaction to patch test and flare up of existing lesions in many instances
- (f) Relief on avoiding allergens, reappearance on re exposure
- (g) Allergens are not antigens (evoke no antibodies) They are simple chemical substances, plant oils, products of fungi, or bacteria and rarely protein

It was in 1933 that Fournau and Bovet first showed that synthetic compounds related to phenolic ethers had the ability to counteract histamine in vitro and vivo Since then many compounds have been and are still being synthesized The compounds most efficient were found to be the following

- I 929F (Fournau Compound)
- II 1571F (Staub's Compound)
- III 2325 R P
- IV 2339 R P (Antergan) both introduced by (Mosnier)
- V 2786 R P Neoantergan or Anthisan (Bovet & his associates)
- VI A524 (Benandryl)
- VII C63 Pyribenzamine (Ciba)
- VIII Antistine (Ciba) (Meier & his associates)

All of them contain a benzene ring linked with certain other radicals and the difference between them is an addition of a new radical to one or substitution of another or deletion or both Of these the first two have been found to be very toxic and were given up The II and III also were given up due to their toxicity Of the remaining four Neoantergan is the most powerful but a little more toxic than the others and of the remaining three Antistine (Ciba) and Pyribenzamine (Ciba) were found to be the least toxic But if potency and non-toxicity were taken into account the most potent and effective of the drugs mentioned above is Pyribenzamine (Arbesman)

Properties and Pharmacology —Soluble in water All of them have a local anaesthetic action more powerful than novocaine, but irritating later on a Quinidine like action on the heart more powerful than Quinidine itself They specifically counteract most physiological effects of histamine Thus they counteract whealing They have been found to raise Blood Pressure lowered by histamine in dogs They prevent contraction of intestinal and uterine muscle strips caused by histamine in guinea pigs both when the drug is added to the perfusing fluid and administered to intact animals before experiment They prevent death from lethal doses of histamine in experimental animals Clinically the most striking effects are the inhibiting whealing and drying up of secretion caused by histamine, a significant point, since excessive secretion is a cardinal feature both in allergic rhinitis and asthmatic attacks It has also got an antispasmodic action which appears to have three components —

- (a) An antihistamine like action
- (b) An antispasmodic like action
- (c) Anti-acetylcholine like action

It has also been described to have an atropine like action when a solution is applied to the eye (Swartzberg & Willerson) Another effect of these drugs is a hypnotic one, more marked in some drugs like Benadryl and less so in others like Pyribenzamine

Mode of Action —Based on the observation that the amount of histamine antagonised bears a quantitative relationship to the amount of antihistamine drug injected, it is believed that the drug competes with histamine for a site of action or receptive substance in the same way as para-aminobenzoic acid competes with sulpha drugs

Dosage —Initial dose 50 mgr repeated thrice daily may be given up to 1200 mgr total per day according to clinical improvement and tolerance of the drugs Children tolerate the drugs well for instance a clinician has given 25 mgr Q D S in a four month infant without any untoward effects, and 50 mgr Q D S in six years old children But usually the dose in children is computed on the basis of 2 mgr/lb body weight per day, the total being divided into two or four doses

Routes of administration —

- (1) Oral
- (2) Parenteral {
 - Subcutaneous
 - Intramuscular
 - Slow intravenous
- (3) Topical in the form of ointments, pastes and creams (2% Finberg) & Iontophoresis

Skin Diseases in which encouraging Results have been published — Urticaria, angioneurotic edema, certain itching dermatoses, general and local, such as atopic dermatitis, eczema, pruritus due to various causes, pruritus of the genitalia, and of the anus, dermatitis medicamentosa, serum sickness type of reaction due to sulpha drugs and antibiotics Some not relieved by oral administration were relieved by injection Finberg gives four cases of angioneurotic edema not amenable to oral treatment were controlled by I V antihistamine drug, the dose being 10 mgr intravenous first, then two hours later 30 mgr, then 30 mgr. four hourly for two days

Untoward Effects —Headache, dizziness, tinnitus, drowsiness, sleeplessness, blurred vision, pupillary dilation, confusion, stupor, narcolepsy, somnambulism, light vertigo, ataxia, acute melancholia. Bad taste, dryness of mouth and nose, epigastric distress, palpitation, weakness, a sensation of relaxation, muscular aching, tingling and numbness of limbs, cold extremities, frequency of micturition, tendency to bleed, facial edema, aggravation of allergic state, acute hysterical condition and lastly collapse

Prevention of toxic Effects and their Treatment —A dosage schedule of the following type will minimise the side-effects. 50 mgr T D S to be increased by 50 mgr /day late in the day, stop increasing the dose as symptoms improve or on the appearance of toxic symptoms, do not increase the effective drug dose for a period of two weeks, at the end of which, discontinue the drug. If symptoms recur treat with 50 mgr T D S, if there is no improvement in 2 days, start with the last effective dose

Parenteral (I V) if mixed with glucose and given slowly side-effects are avoided. If the side effects occur with the first dose it should be decreased to 25 mgr or until a single dose is taken without discomfort. In some, giving a single dose at bed time two or three days before starting the dosage schedule, has controlled side effects. In others giving the drug on a full stomach with sugar and soda bicarb has helped. Severe side reactions can be controlled by Pyridoxine 25 mgr. For intractably severe reactions I V 0.5 mgr iflustramine acid phosphate has been recommended as the specific antidote. Recently, the hypnotic effect has been counteracted by Benzedrine 5 mgr by mouth given early in the morning

Dosage Schedule —

Days	Breakfast	Lunch	Supper	Bed-time
1	50	50	50	nil
2	50	50	50	50
3	50	50	50	100
4	50	50	100	100
5	50	100	100	100
6	100	100	100	100
7	100	100	100	150 & so on

Clinical trials in Dermatology with percentage of effectiveness

(Various Authors)

Cases where encouraging results have been seen but insufficient number tried are pruritus vulgaris, pruritus due to various causes, neuro dermatitis, pruritus vulvae and ani, dermatitis medicamentosa lichen planus psoriasis, erythema multiforme, mycosis fungoides urticaria papulosa (where itching was relieved). Other cases tried with reported failures are cheilopompholyx, actinic dermatitis, pityriasis rosea, infantile eczema, pemphigus vulgaris etc. Reports on the clinical use of antihistamine drugs in chronic urticaria show that some patients are not relieved. Of a total number of 490 cases tried, 91 were not improved (Improved 71.5% and failures 28.5%)

More recently these drugs have been tried in the following diseases -

Scleroderma & Acrosclerosis —Favourable results were noted and stiffness was relieved 22% sustained results were noted in Acrosclerosis

Acute lepra Reaction and painful Neuritis (Wharton) —Were relieved in 24-48 hours with these drugs where other remedies had failed. He attributed its action to the assumption, that the symptoms of lepra reactions are dependent on histamine being set free in the blood

Topical Application —It has been shown that the local use of a solution of an antihistamine drug to a scratch, inhibits the normal whealing due to histamine, much better than when the drug was given orally. It has also been shown that a solution of antihistamine drug can penetrate unbroken skin. Stroking the part on which an antihistamine drug was applied in dermographic skin showed whealing in the control side but no whealing on the treated side. Finberg tried 2% Pyribenzamine ointment in a water soluble anhydrous base in 33 cases of atopic dermatitis in various stages. 24 (72.7%) showed consistent relief. Improvement was more marked if the drug was also given by mouth. Of 9 cases of pruritus and 8 cases were relieved with local application (88.8%)

CLINICAL TRIAL

Antistine and Pyribenzamine were tried in a series of 96 cases in which pruritus was an important symptom

Urticaria and Anglo-Neurotic oedema —There were 29 cases in this series. It was found that the greatest relief was obtained by those suffering from urticaria. In two cases relief was dramatic. The wheals disappearing within two hours. The urticaria in both these cases had been brought on by Penicillin, which was naturally stopped. In one of these cases, Penicillin therapy was restarted after symptoms had been absent for 24 hours. The patient was given 100,000 units in four equally divided doses at four hourly intervals. Half an hour before each injection, one tablet of Antistine was given. No wheals occurred, although there was a mild amount of itching after the fourth injection.

Twenty two of the total number of cases got complete relief, five were sufficiently relieved, to discontinue treatment and two derived no benefit from either drug. In all these cases, the only other treatment given, was a Calamine lotion. In 3 cases, the urticaria was due to a food allergy although temporarily relieved, recurred until the offending food stuff was omitted from the diet.

One case followed the injection of Anti-tetanic serum and relief was obtained only when the dose of Antistine was stepped up from four tablets a day to eight tablets a day, on the third day of treatment. On the fourth day, the dose was diminished to three tablets only as the patient complained of dizziness, nervousness and epigastric discomfort. On the fifth day as symptoms showed a tendency to return, the patient was given an intravenous injection of 100 mg diluted in 25 c.c. of glucose. He had no symptoms that day, nor were there any side effects from the drug. On the sixth day, the injection was repeated and the patient was then discharged as cured.

An elderly patient (aged 72) with Anglo-Neurotic oedema was prescribed Antistine orally. After the first tablet, he complained of

nervousness, dryness, of the mouth, tremors of the hands and a feeling of great depression. His pulse became feeble, and he (and his relations) appeared to be much distressed. He was prescribed Coramine and after a few hours recovered. It was decided to discontinue Antistine. As the Angio-Neurotic oedema had not been relieved he came up for treatment again and as so often happens in a busy department, he was seen by a House man who had no knowledge of the patient's previous experience with Antistine. He yielded to the patient's demand for an injection by ordering 100 mg of the drug to be given by the intravenous route. Remarkably, the patient was much relieved, the oedema subsiding completely when he came up for observation next day. There were no side effects.

Two cases of Angio-neurotic oedema were put on Antistine for four days. The dose was stepped up to an extra 100 mg daily by intramuscular injection for the next three days. Neither of these cases was relieved and it was decided to discontinue the drug. These were the only two failures, in the series of 29 cases. Antistine was given to 20 patients and Pyribenzamine to nine.

Atopic Dermatitis —Twelve cases in all were treated. Eight of them had infantile eczema, and ranged between six months and two years in age. Twenty five mg of Antistine, four times a day, was well tolerated by all except one, in whom it had to be discontinued owing to persistent vomiting. There was apparently no relief from symptoms in any of the cases. In two cases, where there was no oozing, an ointment containing 800 mg of Antistine to the ounce, was also applied without obvious change. Admittedly, it is difficult to assess the degree of relief in very young children.

Four cases occurred in older children with flexural eczema (Besnier's type). They were given on an average 50 mg four hourly. Two of the cases expressed benefit of moderate degree. The other two were unaffected. All four were then put on Antistine ointment on one side and a 3% Tar ointment on the other. Three patients preferred the Antistine whereas one was more comfortable with the tar.

Constitutional Eczema —Twenty three patients with eczema, which used to come on in seasonal attacks for years, were put on Antistine (16 patients) and Pyribenzamine (7 patients). In the Antistine group, four patients expressed relief in 24 hours, after being given 200 mg. Six were relieved within 48 hours on a similar daily dosage plus 100 mg by intramuscular injection. The remaining six expressed no appreciable change. In the Pyribenzamine group, results were fairly similar, four patients being relieved and three were not much affected. All the patients who reacted favourably to the drugs, expressed their belief, that the duration of their attacks had been definitely curtailed. Only three patients in this group complained of mild side effects which disappeared after persisting with the drug.

Neuro dermatitis (with lichenification) —Eight cases of this type were treated with Antistine. An average dose of 150 to 200 mg by mouth was given to each patient without appreciable effect. One of these patients, complained of dizziness and vomiting and after the third day, treatment was discontinued. Three patients were given an additional 100 mg daily, by the intramuscular route, but no relief

was obtained. These same three were then put on an Antistine containing ointment and two of them obtained a slight measure of relief.

Urticaria Papulosa — One case occurring in a child of three came under observation. 25 mg four times a day was given for the first 48 hours. There was no apparent relief, however, and the dosage was stepped up to 50 mg four hourly. This was quite well tolerated and after 2 days on this dosage, itching was definitely reduced. The drug was continued for a further 8 days, the patient then discontinuing treatment, as he was quite well.

Contact Dermatitis — Five patients working in a chemical factory, all appeared together for relief from a dermatitis of the face, neck, forearm and hands. Each was put on 4 tablets of Antistine daily for two days. One of them was much relieved. One other patient had some epigastric discomfort and nausea. The drug was reduced in his case to 1 tablet four times a day and he was given an additional 100 mg by intramuscular injection twice daily. Great relief was obtained in his case. After three more days on this treatment he was discharged cured. In the remaining four patients the dose was pushed up to 6 tablets a day and after a further four days, all four of them said that they were feeling much better. The rash had completely subsided. However, as the source of irritation had been removed from the first day of their attendance, it is probable that the relief was partly due to this fact and to the Calamine application they were given. On the other hand, Antistine definitely helped recovery as after taking it the itching was immediately relieved.

Infective Eczematoid Dermatitis — One female patient was admitted with a history of an injury to the foot, which had got infected and set up a local eczema. Two days previous to admission she developed erythematous patches with slight oedema of the face and upper limbs. She was put on six tablets of Sulphathiazol and on the following day, oozing commenced in the affected parts with severe itching and burning all over the body. There was a vesicular eruption on the sides of the fingers and the backs of the hands. Sulphathiazol was stopped and Antistine 100 mg by intramuscular injection and 6 tablets daily by mouth was given to her. Within the first 24 hours, the itching and burning had appreciably diminished and in a further 24 hours had almost completely disappeared. Locally, the Calamine lotion had been used throughout. On the foot a 4% Sulphathiazol ointment was used during the first 24 hours, but as it was suspected that the aggravation of her symptoms was due, at least partly, to sensitivity to Sulphathiazole, it was changed to a mild mercurial ointment. The patient complained of a bad taste in the mouth and loss of appetite. Antistine was discontinued orally, but she was kept on 100 mg twice a day by injection, for a further three days, by which time she was sufficiently well to be discharged.

Erythema Multiforme — Three cases of Erythema Multiforme were given Antistine 200 mg by mouth per day. Two days without relief. On the third day 100 mg parenterally was given to each besides the oral dose. One patient expressed a moderate degree of relief, the other two were unaffected.

Dermatitis Herpetiformis — Three cases were treated. On the first day they were given 200 mg by mouth without relief. On the second day an additional 100 mg was given by injection and an Antistine con-

taining ointment was applied. On the third day, one patient complained of nausea and epigastric pain and the drug was stopped by mouth but she was given an additional 100 mg by injection. After a further two days as there was no appreciable change, the drug was discontinued.

Pruritus Vulvae —Two cases applied for treatment of his trouble with no detectable cause. One was put on Antistine and one on Pyribenzamine. In addition they were both given an Antistine containing ointment. After 48 hours, both expressed considerable relief and treatment with only ointment was continued.

Pruritus Ani —Three cases of *Pruritus Ani* were given 100 mg orally and an Antistine ointment locally without benefit. After 24 hours an additional 100 mg intramuscular was given to each, one patient expressing a fair amount of relief. No cause was found for the *Pruritus* and after a further 4 days, treatment was discontinued, except for the ointment, in the case relieved.

Lichen Planus —Six cases of *Lichen Planus* came under treatment. One a child aged 14 with an acute attack was given 100 mg on the first day and 150 mg on the second day. Itching was much less and after a further four days had almost completely disappeared. She showed no intolerance to the drug and after a further week of Antistine 100 mg per day, Antistine was stopped. Of three other cases of *Lichen Planus*, two were relieved on 300 mg daily after five days but one showed no relief on similar doses. Two further cases were given Pyribenzamine but without benefit. After four days they were put on Antistine 200 mg per day without further change.

Conclusion —Antistine and Pyribenzamine are undoubtedly of great use in several skin diseases where the relief of itching is an urgent necessity. These drugs find their greatest usefulness in the treatment of urticaria, Angio-Neurotic Oedema and exudative eczema. These antihistaminics are worthy of further trial although they have already definitely acquired a place in the relief of *Pruritus* caused by various types of skin diseases. Side effects were few and never dangerous. The drugs were well tolerated, especially by children, and caused no untoward symptoms when given over a fairly long period of time. One physician—not included in the series—suffered from chronic urticaria of unknown and undiscovered cause for a period of several months. Antistine gave symptomatic and immediate relief, and he was able to prevent attacks by taking one tablet daily $\frac{1}{2}$ hour before the attack came on—usually about six p.m. every day. He continued this for 3 months, during which any day the tablet was omitted, on came the attack. Eventually after the 3 months on Antistine he was free from further trouble and is still free, four months after discontinuing treatment.

REFERENCES

- Allergy in Practice by Samuel Finberg
 Year Book General Therapeutics 1947
 United States Dispensary 24th Edition
 Lancet May 17 1948
 „ December 18 1948
 „ February 12 1949
 B M J May 8 1948
 Overseas Post Graduate Journal April 1948

Critical Notes and Abstracts

SALT DEPLETION

The recognition of the importance of the retention of sodium in the aggravation or in the production of the phenomena of congestive heart failure has directed attention to methods that will diminish the sodium content of the body in the therapy of disorders characterised by these phenomena. Two procedures are used to accomplish this purpose. One procedure consists of a diet that is poor in salt, and the other is the use of powerful diuretics that produce a disproportionately greater excretion of sodium chloride than of water. Soloff and Zatuchni, in a recent article discuss these procedures in detail, and though they do not doubt the efficiency of such regimen in improving the prognosis and relieving the patients, they point out the limitations to its use.

Seven cases are briefly reported that demonstrate some of the untoward effects, including four fatalities, which may occur in cardiac patients subjected to a regimen of sodium restriction and sodium diuresis. Salt substitute was not used by any of these patients so that neither lithium nor potassium intoxication had to be considered as a possible aggravating factor. The blood urea nitrogen was determined in seven patients, the blood chlorides in six patients and the blood sodium in one patient while the phenomena of congestive heart failure were present and while a regimen of sodium restriction and sodium diuresis was still being used. The blood chloride and the blood sodium were reduced and the blood urea nitrogen was elevated in each instance.

Some of these mechanisms which may produce these untoward effects are discussed. Weakness, lassitude, anorexia, nausea, vomiting, restlessness, thirst not relieved by plain water, apathy, mental confusion, fall in blood pressure, increase in pulse rate, diminution in the volume of the pulse, clammy skin, shock and coma are all symptoms or signs which may be present in excessive salt depletion.

The great advance in therapy of heart disease by the introduction of a regime of sodium diuresis is emphasised, but the importance of individualizing this therapy and of being alert to the possibility of the patient's having passed from the therapeutic to the toxic stage of this therapy is particularly stressed.

(Soloff Louis A. M.D., Philadelphia Pa. & Zatuchni Jacob M.D. Syndrome of Salt Depletion. *Journal of the American Medical Association* 139: 1130 April 1949.)

VITAMIN E IN ANGINA PECTORIS

A recent study by Ravin and Katz attempted to evaluate vitamin E therapy on a small, carefully selected group of patients suffering from angina pectoris. All patients were systematically investigated in the usual fashion with history, physical examination, routine blood counts, blood Hinton test, electrocardiogram and x-ray of the heart. On three separate occasions, at weekly intervals, they were given the two-step test before being started on vitamin therapy.

In this way a base line of performance was established. After suitable control determinations had been made, each patient was given 250 mg. of vitamin E, to be taken twice daily, in the form of natural mixed tocopherols. During the course of the investigation patients were required to avoid the use of mineral oil, or cod liver oil, as well as

any iron preparations, which might inactivate the vitamin. The patients were studied by an exercise-tolerance test, and note was made of any subjective or objective change during the course of treatment, which varied from four to 24 weeks. In only one case was there even slight objective benefit.

Since the method of assay of the alpha tocopherol content of vitamin E is considered controversial and some workers maintain that biologic assay is the only reliable procedure, these points remain to be proved conclusively. At present they represent items of possible controversy attempting to reconcile the results of the current study with those of others who have reported almost uniform benefit from vitamin E in as short a period as a few days to a few weeks.

(Iver S. Ravin, M.D., Boston, Mass. and Kermit H. Katz, M.D., Vitamin E in the Treatment of Angina Pectoris, *The New England Journal of Medicine* 240: 331, March, 1949.)

GREATER APPRECIATION OF PROTEIN

The constantly changing picture of the science of nutrition is reviewed by McLester in a recent article discussing the merits of protein. The general attitude toward nutrition was usually in accord with the trend of research and the dominating ideas of a particular era. This development can be divided into five periods, all culminating today in a period of greater appreciation of protein. During the era of the great pioneering students of metabolism, consideration was given to energy exchange, and attention to calories was of primary importance.

Physicians of the early years of the 19th century gave little thought to the nutritive requirements of the sick person, and the disastrous effects of such a diet were not appreciated until the first decade of this century. Studies of typhoid fever and gastric ulcer showed the distinct advantage of a more liberal diet. The third era brought protein into disrepute, and it is just now recovering its good name. This was the era of economy in nutrition. Studies on protein restriction gave support to the supposition that a low protein diet enabled a person to maintain better health and a greater degree of vigor. However, there were two faults which tended to make the conclusions fallacious, first, control groups were not used, and second, the time element was entirely too short.

The fourth era, the most colourful of all, reawakened the interest of the public and professional men in deficiency diseases, this was the vitamin era. At the present time, however, the picture is changing, and recent experiments and the trend of research indicates a new appreciation of the value of protein. The part played by protein in the metabolism of the cell has been greatly clarified and some of the older concepts are being radically revised. The present opinion is that the proteins of the body cell are not fixed parts of a permanent structure but are labile substances in a constant state of change.

Recent research recommends adequate protein for the pregnant woman and surgical patient. Protein therapy is being used in treatment of infectious hepatitis, nephritic patients, and in the diets of patients with peptic ulcer. There has been a dramatic about face accomplished in the recent history of nutrition.

(McLester, James S., M.D., Birmingham, Ala., Protein Comes Into Its Own, *Journal of the American Medical Association* 139: 897-902, April, 1949.)

THE PROBLEM OF PEPTIC ULCER

Data indicating that ulcer recurrences are so frequent in all types of medical practice that with some exceptions peptic ulcer should be considered an incurable disease has been given by Althausen, who urges control by appropriate measures. Dissatisfaction with the present handling of the problem of peptic ulcer should be directed not so much at the results of medical treatment of the current ulcer as the failure to prevent recurrences.

Recurrences of peptic ulcer are associated with four main "inciting" causes. Physical and mental fatigue, emotional disturbances, dietary indiscretions, and respiratory infections. Preventive measures consist of (a) Elimination of overwork and adjustment of occupational predicaments. (b) Attention to psychosomatic factors. (c) Precautions in regard to diet and so-called "stimulants." (d) Prophylaxis and therapy of respiratory infections. (e) Institutions of a protective regime during periods of unavoidable stress. (f) Prompt treatment of recurrences of epigastric distress.

Prevention of ulcer recurrences should start with proper diagnosis and adequate medical treatment. Failure of physicians to insist on a strict and sustained regime decreases the percentage of successful cases and results in early recurrences of peptic ulcer which eventually lead to serious complications. This applies particularly to patients with low sensitivity to pain. The surgical operations of subtotal gastrectomy and vagotomy are discussed from the point of view of prevention of ulcer recurrences and of indications for surgical intervention. In man vagotomy counteracts the harmful effects of tension in promoting excessive gastric acidity and motility. On the other hand vagotomy fails at least partly to protect against stimulating humoral influences on gastric secretion, such as histamine, caffeine, alcohol, and nicotine.

From these considerations it appears that vagotomy can be expected to provide less complete protection than subtotal gastrectomy and the degree of protection depends on the cause of hyper-secretion in a given individual. The surgical mortality in the experience of the foremost surgeons is so low that it can be considered as negligible. Even after a successful operation the patient should be urged to observe a medical prophylactic regime, more so after vagotomy than after subtotal gastric resection.

(Althausen Theodore L. San Francisco, Calif. Prevention of Recurrences in Peptic Ulcer, *Annals of Internal Medicine* 30: 544 March 1949.)

DETECTION OF GASTRIC CARCINOMA

A recent study of morbidity and mortality statistics by Roach, Sloan and Morgan has shown that cancer of the stomach is a prevalent and rapidly fatal disease, for which the only promising form of therapy available today is surgery. Approximately 60,000 men and 42,000 women above the age of 40 develop gastrointestinal malignancy each year in the United States. Of these, almost 60 per cent die within one year of the time that the diagnosis is made. Moreover, those individuals who do not survive the disease comprise nearly one half of the deaths resulting from all types of cancer and 5 per cent of the deaths occurring from any cause.

According to the statistics published by Dorn, the average length of life following the recognition of the disease is of the order of

and eight months regardless of therapy. It is evident, therefore, that the methods currently employed in the diagnosis and treatment of cancer of the stomach are, in general ineffective. Radiation therapy has been uniformly unsuccessful because of the high resistance that gastric neoplasms exhibit toward any of the radiations which have been available to this time.

If surgery is to be successful resection must be done early in the course of the disease, prior to the appearance of symptoms. Thus, methods must be developed whereby large segments of the population may be examined at regular intervals to find the asymptomatic but positive case. The most feasible method for carrying out this sort of an examination is the photo fluorographic process, which has been extremely successful in the early detection of pulmonary lesions. A pilot study has been established to determine the efficiency of this method using the male out-patient population of the Johns Hopkins Hospital above the age of 40. The study will be pursued for a period of five years.

From this study it is hoped that an estimate of the interval at which photo-fluorographic examinations of the stomach should be repeated in the general population may be determined. The study also will determine the reliability of the photo-fluorographic process in the early detection of gastric malignancy, a process that has been virtually untried until the present time.

(Roach John F. Baltimore M.D. Sloan Robert D. and Morgan Russel H. The Detection of Gastric Carcinoma by Photofluorographic Methods. *American Journal of Roentgenology and Radiation Therapy* 61: 188 February 1949. Dorn H. F. Illness from Cancer in the United States. *Public Health Reports* 1944: 59: 33-48, 65-77, 97-115.)

HEPATIC BLOOD FLOW IN MAN

A recent detailed analysis of hepatic function and dysfunction in man by Bradley assigns to the liver a role of importance not only in metabolic activities but also in cardiovascular dynamics, since it provides with the kidney, a kind of hemodynamic buffer against undue stress. The liver acts as a selective barrier between the gastrointestinal tract and the systemic circulation, metabolizing, detoxifying and elaborating for further physiologic disposition various substances that enter the portal blood during digestion. The complex vasculature of the liver serves these processes by providing an adequate supply of oxygen and raw materials.

The recent development of methods for the atraumatic catheterization of the great veins by Cournand and his co-workers at Bellevue Hospital has provided a means by which hepatic venous blood may be sampled at frequent intervals in human subjects without difficulty. By this method a long, radio opaque ureteral catheter may be inserted into an antecubital vein, and passed under fluoroscopic control through the superior vena cava and right atrium into the inferior vena cava and thence into one of the right hepatic veins. The hepatic extraction of various substances may be measured directly, and hepatic blood flow estimated by a clearance technique, thus opening vast new field of study and exploration. Bromsulfalein is being used in the clearance technique, since it is removed from the blood almost exclusively by the liver.

The EHBF (estimated hepatic blood flow) is a measure of volume of blood flowing into the splanchnic vasculature each minute, without reference to the relative contributions of the mesenteric, splenic, gastric and hepatic arterial inflows. In 50 normal resting human subjects

studied at the Evans Memorial Hospital in Boston, EHBF ranged from 950 to 1840 c c per minute per 1.73 M^2 of body surface, averaging 1490 c c per minute. Approximately 25 per cent of the basal cardiac output appears to pass through the splanchnic circuit.

Studies of the hepatic circulation indicate that the liver also plays a prominent role in vascular homeostasis. The variability of the blood flow in animals is attributed to irregularity of blood flow through the sinusoids. A study of hepatic circulatory dynamics during exercise was undertaken in collaboration with Dr E. DeF. Baldwin at the Columbia Presbyterian Medical Center for the purpose of assessing integration of the hepatic circulation into the total circulation during stress. Although little change in blood pressure occurred during exercise, the output of the heart almost doubled. At the same time the blood flow through the kidney and the liver fell sharply, the hepatic blood flow to a much greater extent than the renal.

The blood flow to other circuits—the brain, heart and especially the muscles increased to a greater extent than is indicated by the change in cardiac output. In this way blood was made available at the expense of the liver and kidneys while the heart was spared the effort required to expel sufficient blood to meet the total need imposed by exercising muscle. It is evident that complete exploration of the hepatoportal circulation is indicated.

(Bradley, Stanley E. New York City, N.Y. Variations in Hepatic Blood Flow in Man During Health and Disease. Cournand, A. and Ranges, H. A.: Catheterization of Right Auricle in Man. *Proceedings of the Society of Experimental Biology and Medicine* 46: 402, 1941.)

NATURAL RESERVOIR OF POLIOMYELITIS

Four anticipated features of a natural host for poliomyelitis would be

- 1 That it will be found throughout the temperate and tropical zones
- 2 That it will account for the frequently observed tendency of the disease to start and to have a higher incidence in rural than in urban populations
- 3 That it will account for the seasonal tendency of the disease in man
- 4 That it will be so inconspicuous as to have escaped consideration to date

After considering the fossorial habits and the geographic distribution of the ground mole, the possibility of this animal fulfilling the four anticipated features of a natural host for poliomyelitis was discussed by Reector in a recent article. It is obvious that a higher percentage of the rural than of the urban population comes in contact with these animals, yet the prevalence of moles in the city parks offers urban dwellers sufficient contact with them disregarding trips to the country. Furthermore, spots maps of urban epidemics of poliomyelitis frequently show a centripetal spread.

Successful passage of the virus from mole to mole and from mole to Swiss mouse and cotton rat is reported. Attempts to pass the virus to three monkeys have been unsuccessful, however. Forty-three moles have been exposed to, or inoculated with, virus of poliomyelitis obtained from the following sources: mouse brain experimentally infected with the rodent-adapted strain of Lansing virus, brain and spinal cord of a

human patient who died of poliomyelitis, and stools of four infected human beings. Of these animals, but two have survived.

Two distinctly different types of terminal behaviour are described. The survival time of the infected animals is unpredictable, regardless of the source of the inoculum, the route of inoculation or the relative position of the animal in serial passage. There is not any tendency of the virus to become fixed. Possible routes of inoculation other than intracerebral have not been adequately investigated. The absence of typical histopathologic lesions of poliomyelitis in the moles and the Swiss mice and cotton rats in which passage of mole brain and spinal cord was effective is discussed, however the lack of such lesions is not unique in the mole, since the pathological condition observed in rabbits and monkeys does not duplicate that of the usual human or simian lesions.

Fifteen animals were employed as controls for comparative studies of autolytic changes, dietary deficiency, ability of the mole's brain to respond with mobilization of inflammatory cells, trauma of handling and reaction to foreign protein. Investigation is still in progress concerning such questions as to which strains of virus the mole is susceptible, by what routes of inoculation infection is possible, whether the mole flea is a vector or possible intermediary host and the possibility of eventually producing lesions.

(Rector L. E., M.D., St. Louis Mo. The Mole as a Possible Reservoir of Poliomyelitis. *Archives of Pathology* 47: 306 April, 1949.)

INDICATION OF EARLIER STAGES OF HUMAN HYPOXIA BY ELECTROENCEPHALOMETRIC MEANS

Among the electroencephalometric features studied by these investigators, the most reliable means of indicating hypoxia is an increase of those 5-7 c/s waves which appear in trains of two or more. Only two out of 107 subjects failed to show this increase before marked mental disturbances could be recognized, and it is believed that even these failures can be prevented when a modification in frequency characteristics of the measuring equipment has been done.

For an altitude of 25,000 feet, a postwarning safety interval of at least 60 seconds then can be expected in all of the normally reacting subjects and for 88 per cent of these the value is even greater than 90 seconds. In fainting types an almost simultaneous occurrence of warning and breakdown must be expected. On account of the method used, hypoxia could be indicated earlier than previously has been done by the usual procedure of visually inspecting the EEG record. The measurements presented in this paper were accomplished with an anoxia indicating the warning device. The results are in favor of its practical applicability.

(Prast Johannes W., and Neell Werner K. Indication of Earlier Stages of Human Hypoxia by Electroencephalometric Means. *Journal of Aviation Medicine* 19: 426-434 December 1948.)

HYPERTENSION AND TACHYCARDIA DUE TO CONCUSSION OF THE BRAIN

The neurovegetative manifestations, observed in the two cases of cerebral concussion reported by this author, differ in certain respects. The first patient developed a sustained hypertension which persisted for several weeks and declined gradually. It was accompanied by a permanent tachycardia but no significant elevation of temperature which would have been attributable to the cerebral injury as such.

In the second patient there were numerous paroxysms of hypertension, tachycardia and hyperpyrexia, alternating with fairly normal conditions, except for some mental disturbances, and subsiding spontaneously, only to be provoked anew and for a much longer period by a second concussion

The symptoms and signs resemble those which have been described in some cases of brain tumors located near the third ventricle (diencephalic autonomic epilepsy), in cases of encephalitis and of poliomyelitis of the upper medulla oblongata and in cases of essential hypertension and hypertension induced by pheochromocytoma. A comparison of the symptomatology of these hypertensive syndromes with the ones due to cerebral injury suggests that all of these syndromes have certain neurovegetative features in common which may be attributed to an excess activity of sympathomimetic amines, epinephrine sympathin, and encephalin

(Raab Wilhelm Burlington V1 Hypertension and Tachycardiac Due to Concussion of the Brain American Heart Journal 37 237 248 February 1949)

INFECTIOUS MONONUCLEOSIS AND INFECTIOUS HEPATITIS

This report presents a study of 35 patients with clinical features and laboratory findings consistent with infectious (viral) hepatitis and infectious mononucleosis. Twelve acutely ill patients were carefully selected to point out certain resemblances and differences in the two disorders. According to the authors a serial study of heterophile antibody behavior, the flocculation tests, and certain hepatic function tests in these disorders indicated the following resemblances and differences

(1) Significant increases in heterophile antibody titer occur only rarely in infectious hepatitis in contradistinction to infectious mononucleosis

(2) The agglutinin in the serum of cases of infectious hepatitis differs from that in infectious mononucleosis in its absorbability by guinea pig kidney

(3) In both infectious hepatitis and infectious mononucleosis the serum flocculation tests (cephalin cholesterol, colloidal gold, thymol turbidity and 18 hour turbidity ratio) show a marked tendency to be positive early and to remain positive for long periods

(4) Liver function measured by the ratio of esterified to total cholesterol is far less often abnormal in infectious mononucleosis than in infectious hepatitis. Sulfobromophthalein excretion is also only occasionally abnormal in infectious mononucleosis

(5) It is suggested that in infectious mononucleosis, even more clearly than in infectious hepatitis, the flocculation phenomena are associated primarily with alterations in the serum proteins and perhaps lipids. They would appear to be related to the liver changes in the disease only insofar as the latter contribute to the alterations in the protein and lipid components of the serum

(6) Serum alkaline phosphatase shows increased activity in most cases of both infectious mononucleosis and infectious hepatitis during the first month of disease. However, since most of the mononucleosis cases were not jaundiced while all of the hepatitis cases were jaundiced,

the mechanism responsible for hyperphosphatasemia may not be identical in these disorders. The degree of elevation of a serum alkaline phosphatase in non-jaundiced patients with infectious mononucleosis may occasionally be pronounced.

(Berk, J. Edward Philadelphia, Pa., Shay Harry Ritter Joseph A., and Siplet Herman. Infectious Mononucleosis and Infectious Hepatitis. Studies Bearing on Certain Resemblances and Differences. Gastroenterology, 11: 658-671 November, 1948.)

Book Reviews and Notices

ECTOPIC PREGNANCY by Dr K. M. Masani M.D. (Lond.), F.R.C.S. (Eng.) Pp 165, Price Rs 12/-. THE POPULAR BOOK DEPOT, BOMBAY 1949

The book is written in seven chapters, each one dealing with a different aspect of the subject. In the first chapter the author has given in chronological order the various milestones in the evolution of the present day knowledge of the subject. They are described thoroughly well and yet so briefly that its reading becomes untiring, interesting and inspiring. History of the evolution of the theories, investigations and research of a scientific subject is the basis for its future progress. Thus Dr Masani has given admirably well.

Subsequent chapters deal with the aetiology, pathology, clinical signs and symptoms and treatment of the complication. In the last chapter notes of a few cases have been included as specimens demonstrating unusual pathological and clinical features which might tax ingenuity of any obstetrician correctly and quickly to diagnose the complication.

Each chapter is written in detail, reviewing and analysing up-to-date literature on a particular aspect of the subject. Dr Masani has brought to bear on his conclusions his own work at the K. E. M. Hospital and that of other Indian obstetricians.

In spite of this he has kept himself within reasonable limits of briefness. Though there has been an enormous literature built up on the subject there is dearth of such volumes as would present a comprehensive survey of all that mass of knowledge. Dr Masani, by bringing out such a volume, has filled this deficiency. The book will be very useful to the postgraduates. Obstetricians and research workers will find in it much interesting data and useful guidance. The book is a welcome addition to the libraries of institutions and of individuals interested in the subject. It is printed on art paper in fairly good size type and contains some illustrations of unusual specimens. The general get-up is pleasing. All these features make the reading of the book easy, interesting and inspiring. The book can be confidently commended to students, pathologists and obstetricians.

CHAMANLAL MEHTA

The Indian Physician

VOL VIII NO 10

OCTOBER 1949

WHOLE NO 94

Original Contributions

A STATISTICAL STUDY OF 1281 CASES OF CONGESTIVE CARDIAC FAILURE OR MYOCARDIAL INSUFFICIENCY IN INDIA

(FROM A MEDICAL IN PATIENT POPULATION OF 80 104 PATIENTS AT THE KEM
HOSPITAL, BOMBAY)

by

RUSTOM JAL VAKIL M D (Lond) M R C P (Lond)

(From the Cardiological Department, K.E.M Hospital,
BOMBAY)

INTRODUCTORY

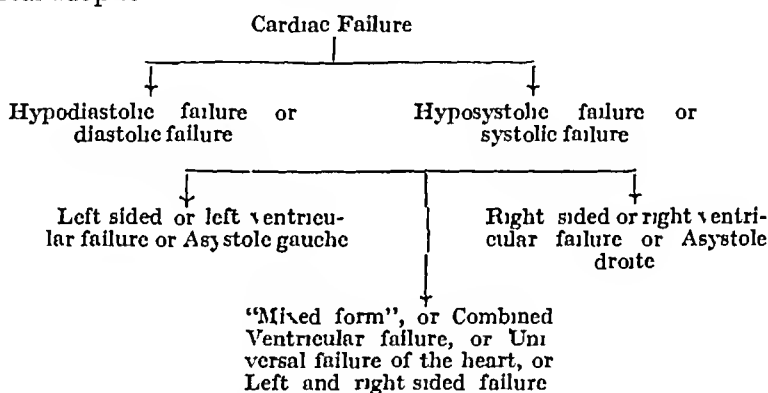
In the opinion of Paul White (1946) "myocardial insufficiency giving rise to congestive heart failure is the commonest of the important functional disorders of the heart"

In order to understand our present day conception of cardiac failure, it is necessary to have an idea of what is meant by "cardiac reserve" or "reserve power" of the heart, these terms denote the "power of accommodation" of the heart to the various stresses and strains of life, a sort of "safety-valve" that comes into operation whenever the body, by indulging in excesses of any kind, tends to overwhelm the heart. With failure of heart, there is a curtailment of this reserve power, if the latter disappears entirely, symptoms and signs of "failure" or "decompensation" of the heart become manifest even in the "resting state," quite apart from exertion.

"Cardiac failure" or "myocardial insufficiency," has been defined differently by different authors. Beckman defines the condition as a "state of broken compensation in which the heart is no longer able to perform the amount of work necessary if the body as a whole is to maintain a condition of normal activity." Fishburg defines it, from the clinician's standpoint, as a "limitation of the activities of the patient which symptoms or signs reveal to be engendered by defective circulation of the blood." Crighton Bramwell defines it as "an inability on the part of the heart to maintain an output of blood adequate to meet the requirements of the body." Vakil (1946) has given the following definition *viz* "A limitation or curtailment of cardiac reserve (or reserve power of the heart) resulting in an inability on the part of the heart to cope with the demands imposed upon it by the body."

Many different *classifications* of cardiac failure have been proposed in the literature, only to be rejected subsequently on the grounds of being unsuitable or inadequate. The tendency for the majority of British cardiologists is to consider cardiac failure under the two major divisions of (1) The "congestive form," and (2) The "ischaemic form", the former is subdivided into the following subdivisions viz (A) "with irregular rhythm" and (B) "with normal rhythm". The classification fails to recognize systemic and pulmonary congestion as distinct entities, a distinction of the utmost clinical value, as will be shown presently. Also, this classification makes no attempt at recognizing certain individual "circulatory syndromes" or "symptom-complexes," which are of utmost value from the points of view of both diagnosis and prognosis, they are merely grouped together under the generic caption of "congestive cardiac failure" in spite of their displaying recognizable clinical characteristics.

From the point of view of suitability, the following classification, primarily evolved in France and later modified in America, is deserving of universal adoption.



Cardiac failure according to this classification may arise primarily from a "deficient emptying of the heart during systole" (Hyposystolic failure or systolic failure) or from "inadequate or defective diastolic filling of the cardiac chambers during diastole" (Hypodiastolic failure or diastolic failure), the latter form of failure, in actual practice, is encountered much less often than the systolic form. The systolic or hyposystolic cardiac failure has been subdivided by French clinicians into two distinct syndromes, depending on which ventricle fails first, viz (1) left sided or left ventricular failure, and (2) right-sided or right ventricular failure. To this, may be added, a third form, viz (3) the "mixed form," where both ventricles get affected either simultaneously or one after the other, resulting in a rather complex clinical picture. In hospital practice, where cases are more often than not in a state of advanced disease, this third form of systolic failure is encountered with great frequency (as will be obvious from our data).

Attempts to further subdivide each of the above-mentioned entities into "auricular failure" and "ventricular failure" serve no useful purpose and merely confuse the issue at stake.

Left-sided or left ventricular failure, by resulting in engorgement or congestion of the pulmonary or "lesser circulation," leads to the

following rather characteristic picture *viz* (1) Dyspnoea, which may be paroxysmal and nocturnal (the so-called "cardiac asthma") or exertional or continuous or postural (*i.e.* orthopnoea) (2) Persistent cough, often with brownish expectoration containing the so-called Herzfeshlerzellen or "heart-failure cells" (3) Pulsus alternans, a sure indication of myocardial fatigue or exhaustion. In very rare cases, a corresponding "electrical alternation" in the electrocardiogram, such as has been reported by me in three cases (Vakil, 1946) (4) Gallop rhythm or Brut de galop (5) Absence of oedema, venous engorgement and hepatomegaly, except on rare occasions (5) Signs indicative of pulmonary congestion, such as basal crepitations, "functional emphysema," rhonchi etc (6) Radiological evidences of left ventricular enlargement and pulmonary engorgement (7) A characteristic prolongation of the "arm to tongue" with a normal "arm to lung" circulation time (8) A normal or practically normal venous pressure (9) Diminished "vital capacity" of the chest (10) Attacks of acute or "subacute pulmonary oedema," the so called "exudative form", of pulmonary congestion. Attention was drawn, in 1946, to a common, although neglected symptom complex or syndrome in these cases (definitely commoner than "acute pulmonary oedema" for which the designation of subacute or chronic form of "pulmonary oedema") was proposed (Vakil, 1946)

Right-sided or right ventricular failure, by leading to a systemic rather than a pulmonary congestion, occasions the following clinical picture, *viz* (1) Cyanosis fairly often, (2) Dyspnoea, more often exertional or continuous, (3) Venous engorgement with raised venous pressure. Lewis has described a useful neck-vein sign in this connection, (4) Liver enlargement with tenderness. The Wilham Pasteur or Hepato-jugular reflex may be of diagnostic value, (5) Oedema, which may become generalized, (6) Ascitis or hydrothorax (the latter being more often right-sided)

Mixed Failure or Universal cardiac failure displays an assortment of symptoms and signs, a combination of the individual clinical characteristics of the two forms of systolic failure, described above. Certain forms of cardiac failure with clinical peculiarities have been described in the literature under the designations of "Bernheim's syndrome," "Asystole Hepatique," "Pericarditic form of failure" etc

In 1942 I published a clinical and aetiological study of 600 cases of Heart-failure, observed in Bombay, India (Vakil, 1942). The present paper presents an entirely new and much larger series of clinical cases of cardiac failure, in order to present further insight into this important problem

Aetiological Classification or Grouping of Heart Diseases

General interest in the aetiological incidence of heart disease has been growing rapidly since 1914, when Cabot, in his monumental paper on "The Four Common Types of Heart Disease," focussed for the first time the attention of the medical profession on the value of an aetiological approach to the subject of classification of heart disease

Since that time, much has been said and written on the merits and demerits of this new approach to the heart problem. It is to the Criteria Committee of the American Heart Association that we owe

a debt of gratitude for putting the whole matter on a workable footing. Besides presenting a comprehensive classification of Diseases of the Heart, along aetiological lines, they have standardized the procedure of allocating heart-cases to their respective classifications. For the purpose of the present paper, we have adopted the classification of the Criteria Committee (except for a few necessary modifications here and there).

Objects of study The main objects of the present study were (1) To determine the frequency or incidence of cardiac failure cases in India (2) To determine the exact role or relative incidence of different aetiological factors in the causation of cardiac failure (3) To determine the relative incidence of the types of cardiac failure in different aetiological groups of heart disease (4) To analyze the mortality rates of cardiac failure cases in the different aetiological forms of heart disease.

Selection and Nature of Material

During the five-year period, from 1941 to 1945 (inclusive) 80,104 medical inpatients were treated at the K E M Hospital, Bombay. A critical survey of the case records allowed us to sort out 1860 cases of "organic heart disease" for further statistical study (giving an incidence of 6.2%).

Results of investigation

There were 1281 cases of cardiac failure in our series of 1860 cases of cardiovascular heart disease, giving an incidence rate of 68.8%, in other words, over two-thirds of our cases of heart-disease also displayed cardiac failure.

There were 1281 cases of cardiac failure in a medical in-patient population of 80104 patients at the K E M Hospital, i.e. an incidence of 4.8% of all medical admissions. That is, one admission in every 28 at the K E M Hospital, displayed cardiac failure.

Aetiological Grouping of our cases

In accordance with the Report of the Criteria Committee of the American Heart Association on the Aetiological grouping of heart-disease, 1281 cases of cardiac failure in our series, were classified as follows —(See Table I)

TABLE I
AETIOLOGICAL CLASSIFICATION OF HEART FAILURE CASES
(1281 cases)

Aetiological group		No. of Failure cases	Percentage Incidence
1	Congenital	8	0.6
2	Rheumatic	375	29.3
3	Syphilitic	150	11.7
4	Bacterial	7	0.6
5	Hypertensive Coronary	400	31.3
6	Pulmonary	119	9.3
7	Miscellaneous and Unknown	222	17.2
All Cases		1281	100.0

It will be observed from Table I, that under the joint-designation or caption of "Hypertensive-Coronary" we have included two distinct groups of cases *viz* cases of hypertensive heart disease and cases of coronary artery disease. This proved necessary because of the large "overlap" between these two groups, a very large number of cardiac cases exhibiting hypertensive and coronary disease at the same time.

Throughout our studies on heart disease, the term "arteriosclerotic heart disease" (suggested by the Criteria Committee and adopted by numerous writers on the subject) has been replaced, in accordance with the advice of Sprague and White (1935), by the much more suitable designation of "Coronary Artery Disease" or "Coronary Heart Disease"

In the group marked "miscellaneous," in our Table, are included cases of cardiac failure of diverse aetiological origin, such as thyrotoxicosis, severe anaemias, "beri-beri" or gross vitamin deficiencies, obesity, diphtheria, trauma, kypho scoliotic and other chest deformities etc

In the group marked "unknown," are included cases where we have failed to determine the causative aetiological factor or factors. In India, laboratory facilities are, as yet, not freely available whilst post-mortem examinations are seldom if ever permitted, it is therefore, only natural that many of our cardiac cases remain undiagnosed or unclassified to the very end

Table I illustrates the importance of individual aetiological factors in the causation of heart-failure in India. The following features are particularly note-worthy *viz* (1) The great importance of high-blood pressure and coronary disease, which jointly account for one-third of all the cases (2) Next in importance comes the group of rheumatic heart disease, which accounts for almost 80% of all cases. This high incidence of rheumatic involvement of the heart in the tropics is not sufficiently appreciated by the medical profession. In our experience, the incidence of this disease is not lower than observed in most Western countries (3) The importance of cor pulmonale in the causation of heart failure, accounting as it does for almost 10% of one-tenth of all our cases of failure. Even in Western countries, pulmonary heart disease is said to account for but a small percentage of heart-cases. That such is not the case, at least in India, has already been stressed, previously, (Vakil, 1942) (4) The three major forms of heart disease, *viz* hypertensive, coronary and rheumatic, jointly, account for as many as 60.6% of all our cases (*i.e.* practically two-thirds)

In this connection, we might mention that Boyer, Leach and White (1940) after an analysis of 1000 case of cardiac failure gave the incidence of fundamental causes as follows (1) Hypertension 46.9% (21.8% without and 25.6% with coronary disease) (2) Coronary disease 41.4% (15.8% without and 25.6% with hypertension) (3) Rheumatic heart disease 25.7% (4) Syphilitic heart disease 8% (5) Cor Pulmonale 2.5% (6) Calcareous aortic stenosis 1% (7) Congenital defects 0.7% and (8) Miscellaneous and Unknown 2.57%

TABLE II

The Incidence of Heart Failure in different aetiological groups of Heart Disease

Aetiological Classification	No of cases of heart disease	No of cases of cardiac failure	Percentage incidence of failure in group
1 Congenital	10	8	42.1
2 Rheumatic	401	373	81.5
3 Syphilitic	240	150	62.5
4 Bacterial	20	7	35.0
5 Hypertensive coronary	617	400	64.8
6 Cor pulmonale	188	119	64.0
7 Miscellaneous & unknown	317	222	70.0
All Cases	1880	1281	88.8

Taking all forms of heart-disease, the incidence of heart failure works out at 68.8% (i.e. slightly over two-thirds of all cases)

The highest incidence of failure was noted in the rheumatic group of cases (81.5%). Next in order, came the miscellaneous and unknown group, the hypertensive-coronary group, the pulmonary group and the syphilitic group, with an incidence of 60 to 70%. The incidence of failure was low in the congenital and bacterial groups of heart disease.

Distribution of Types of Cardiac Failure

For all cases Of the 1281 cases of our series, 213 cases (or 16.6%) were Left-sided or left ventricular, 357 cases (or 27.9%) were right-sided or right ventricular and 711 cases (55.5%) were of the "mixed," "universal" or "left and right sided combined" variety.

In other words, over one-half of our cases were of the combined variety whilst only 1 case in six was of the left ventricular variety. In private practice, where early cases of heart disease are the rule, the incidence of left ventricular variety is much higher and surpasses in incidence, the other two varieties.

Distribution of Types of failure in different aetiological groups (See Table III)

Of the 8 cases of congenital heart disease with cardiac failure, 6 had right-sided, one had left-sided and one had the mixed variety of failure.

Of the 375 cases of rheumatic heart disease with failure, the latter was left-sided in 56 cases (14.9%), right-sided in 181 cases (48.6%) and mixed in 138 cases (36.5%).

TABLE III

Distribution of types of failure in different aetiological groups
(Figures expressed in percentage only)

	1 Congenital	2 Rheumatic	3 Syphilitic	4 Bacterial	5 Hypertensive Coronary	6 Pulmonary	7 Miscellaneous unknown	8 All Forms
Left sided	12.5	14.0	18.7	0.0	24.5	1.7	12.0	10.0
Right sided	75.0	48.0	8.0	14.3	2.5	70.5	25.3	27.9
Mixed	12.5	38.0	73.3	85.7	73.0	21.8	62.2	55.6

Of the 150 cases of syphilitic heart disease with failure, the latter was left-sided in 28 cases (18.7%), right-sided in 12 cases (8%) and mixed in 110 cases (73.3%).

Of the 7 cases of bacterial endocarditis with failure, one had right-sided and six had the mixed variety of failure,

Of the 400 cases of hypertensive coronary disease with failure, the latter was left-sided in 98 cases (24.5%), right sided in 10 cases (2.5%) and of the mixed variety in 292 cases (73%).

Of the 119 cases of pulmonary heart disease with failure, 2 had left sided failure (1.7%), 91 had right-sided (76.5%) and 26 cases had mixed failure (21.8%)

Of the miscellaneous group of 222 cases with failure, 28 had left sided (12.6%), 56 had right sided (25.2%) and 138 had mixed failure (62.2%)

Amongst the important groups of failure cases, the highest relative incidence of left ventricular failure was noted in the Hypertensive-coronary group (24.5%) and the lowest in the Pulmonary group (1.7%). The highest relative incidence of right ventricular failure was noted in the Pulmonary group (76.5%) and the lowest in the Hypertensive-coronary (2.5%) and the Syphilitic groups (8%).

The relative incidence of the mixed variety of failure was high in the Syphilitic (78%) groups and low in the pulmonary group (21.8%)

In the case of congenital, rheumatic, and pulmonary groups of heart-failure, right-sided failure was the commonest variety of failure encountered. On the other hand, in the Syphilitic, bacterial, hypertensive-coronary and the miscellaneous groups of failure, the mixed variety of failure was encountered with the greatest incidence. Preponderant incidence of left ventricular failure was not encountered in any of our groups of cardiac failure.

An aetiological analysis of individual forms of Cardiac Failure (See Table IV)

Left sided failure Of the 218 cases of Left-sided failure, in our series, the aetiological grouping of the cases was as follows —

1	Congenital group	1 case	0.5%
2	Rheumatic group	56 cases	26.8%
3	Syphilitic group	28 "	13.2%
4	Bacterial	no "	0.0%
5	Hypertensive coronary group	98 "	46.0%
6	Pulmonary group	2 "	0.9%
7	Miscellaneous & Unknown group	28 "	13.2%

TABLE IV

An Aetiological Analysis of individual forms of Cardiac Failure.
(Figures expressed in case numbers and percentages)

Aetiological group	Left-sided		Right sided		Mixed forms		All forms	
	No	%	No	%	No	%	No	%
1 Congenital	1	0.5	6	1.7	1	0.15	8	0.9
2 Rheumatic	56	26.8	181	50.7	138	19.4	375	29.3
3 Syphilitic	28	13.2	12	3.4	110	15.5	150	11.7
4 Bacterial	0	0.0	1	0.3	6	0.0	7	0.6
5 Hypertensive								
Coronary	98	46.0	10	2.8	292	41.0	400	31.8
6 Pulmonary	2	0.0	01	2.5	20	8.7	110	0.3
7 Miscellaneous & Unknown	28	13.2	56	15.6	188	10.4	222	17.2
All Forms	218	100	357	100	711	100	1281	100

From the above, it will be observed that almost half of all our cases of Left-sided failure belonged to Hypertensive-Coronary group.

About a quarter of all the cases belonged to the rheumatic group Less than 1% of the cases were of pulmonary origin

Right-sided failure Of the 357 cases of right-sided failure, in our series, the aetiological grouping was as follows

1. Congenital group	0 cases	1 7%
2 Rheumatic group	181 "	50 7%
3 Syphilitic group	12 "	3 4%
4 Bacterial group	1 "	0 3%
5 Hypertensive Coronary group	10 "	2 8%
6 Pulmonary group	91 "	25 4%
7 Miscellaneous	56 "	15 6%

From the above, it will be noted that one-half of all our cases of right-sided failure belonged to the rheumatic group whilst one-quarter belonged to the pulmonary group The syphilitic group accounted for only 3 4% of our cases whilst the largest group of all viz the hypertensive-coronary group accounted for but 2 8% of all cases

Mixed Failure —Of the 711 cases of mixed failure in our series, the aetiological grouping was as follows —

1 Congenital group	1 case	0 15%
2 Rheumatic group	138 cases	19 4%
3 Syphilitic group	110 "	15 5%
4 Bacterial group	6 "	0 9%
5 Hypertensive Coronary group	202 "	41 0%
6 Pulmonary group	26 "	3 7%
7 Miscellaneous	138 "	19 4%

From the above, it will be noted that 41% of all cases of mixed failure belonged to the Hypertensive-coronary group The low incidence of the pulmonary group (3 7%) should be noted

Mortality studies of Cardiac Failure cases (1281 cases)

Of our 1281 cases, 352 proved fatal i.e. a death rate of 27 5%. In other words, about one case in every four, admitted to Hospital for Cardiac failure, proved fatal The rest were discharged from hospital either "cured," "improved," "no better" or "against medical advice"

In a previous series of 600 cases of cardiac failure, of diverse aetiology, studied in 1942, (Vakil, 1942) the death-rate was somewhat higher viz 40 3%, 243 out of 600 cases proving fatal

Mortality rates of different aetiological groups (Table V)

From Table V, we observe that the highest death-rate (viz 100%) was noted in the case of the bacterial endocarditis Not one case subacute or acute, admitted at the K E M Hospital in 5 years, left the hospital alive in spite of all efforts at treatment Of the remaining forms of heart-failure, the highest death-rate was noted in the case of chronic pulmonary heart disease viz 44 6% Next in order came the miscellaneous group (37 4%), the syphilitic group (31 3%), the congenital group (25%) and the rheumatic group (23 2%) The lowest death-rate, suprisingly enough, was noted in the case of the hypertensive-coronary group (viz 18 3%), which is often regarded by our profession as being perhaps, the most "deadly"

TABLE V

The Mortality Rates of Cardiac Failure Cases, from the aetiological standpoint (1281 cases)

Aetiological Classification		No. of cases admitted	No. of cases died	Percentage mortality
1	Congenital	8	2	25.0
2	Rheumatic	375	87	23.2
3	Syphilitic	150	47	31.3
4	Bacterial	7	7	100.0
5	Hypertensive coronary	400	78	19.5
6	Cor pulmonale	110	53	48.2
7	Miscellaneous & Unknown	222	63	28.4
All Cases		1281	352	27.5

SUMMARY AND CONCLUSIONS

1 The subject of cardiac failure is briefly discussed from the points of view of definition, classification and clinical recognition

2 A short statistical study is presented of a series of 1281 cases of cardiac failure from a total of 1860 cases of heart disease. Cardiac failure cases accounted for 68.8% of cases of heart disease and 4.3% of all medical cases admitted

3 An aetiological grouping, is presented of our cases of cardiac failure, 81.3% of our cases belong to the hypertensive coronary group, 29.8% to the rheumatic group, 11.7% to the syphilitic group and 9.3% to the pulmonary group

4 The percentage incidence of cardiac failure is determined for each aetiological group of heart disease. In the rheumatic group of heart cases, 81.5% display failure. The corresponding incidence of failure for the hypertensive-coronary group is 64.8%, for the pulmonary group 64% and for the syphilitic group 62.5%.

5 16.6% of all failure cases are of left-ventricular type, 27.9% of the right-ventricular type and 55.5% are of the so called "mixed" or "universal" variety of failure. An aetiological grouping is presented of each variety of cardiac failure.

6 The death-rate for all cases of failure is 27.5%. The death-rate is highest (100%) in the bacterial group, 44.6% for the pulmonary group, 31.3% for the syphilitic group, 23.2% for the rheumatic group and only 18.8% for the hypertensive coronary group.

REFERENCES

- 1 BOYER N H, LEACH C E & WHITE, P D. Pub 13 Am Assoc Adv Sec 1940, p.203
- 2 BRAMWELL, C. *The Principles and Practice of Cardiology*, London, 1942
- 3 COBOT R C : J A.M.A (1914) 63 1481
- 4 FISHERO A M. 'Heart Failure' London 1937
- 5 LEWIS T. Brit Med Jour (1930) 1 849
- 6 VAKIL, R J : Ind Physician (1932) 1 12
- 7 VAKIL R J : Ind Physician (1940) 5 155 5-216 5-247, and 5-253
- 8 VAKIL, R J. Ind Jour Med Sc (1948) 1
- 9 WHITE, P : Heart Disease, New York 1946

THE EFFECT OF SULPHYDRYL COMPOUNDS ON THE IMMEDIATE TOXIC REACTIONS OF NEPTAL

by

H B SWIFT C L MALHOTRA and K N SAREEN

Department of Pharmacology & Therapeutics, Medical College, AMRITSAR

Introduction —In an earlier publication from this Department (Swift and Malhotra), the following conclusions had been drawn regarding the various compounds used in the prevention of the immediate toxic effects caused by intravenous injection of Neptal

- 1 Dilution and slow intravenous injection lessens the toxicity of mercurial diuretics on the heart, but cannot prevent a fatal reaction ,
- 2 Adrenaline can improve the heart poisoned by Neptal ,
- 3 Procaine prevents fibrillation caused by Neptal provided the latter is given in minimum lethal doses ,
- 4 Magnesium sulphate and Quinidine sulphate are not effective in preventing the fibrillation caused by Neptal though the latter delays the appearance of fibrillation

The present study was undertaken to determine if some of the sulphydryl compounds could be effective in the prevention of such toxic reactions. It may be mentioned in this connection, that the compound principally used was BAL (British Anti-Lewisite, 2,3-dimercaptopropanol), but the effects of certain other thiol compounds were also noted. These other compounds were prepared by the chemist of our Department (K N S). As the quantities available were too small for repeated experiments, it is not advisable to draw any definite conclusions regarding these. Further work in this direction is being maintained.

2 *Brief survey of thiol compounds used against intravenous mercurial diuretic poisoning* —In this connection, the work of Farah and Maresh (1948) is very important. They have studied in detail the effects of certain sulphydryl compounds, as cysteine, glutathione, and BAL, etc., on diuresis and renal and cardiac circulatory changes caused by mersalyl, and have come to the following conclusions —

(1) That the diuretic action of mersalyl is counteracted by BAL and is abolished by the administration of half a molecule of BAL for every molecule of mersalyl ,

(2) That cysteine and glutathione do not interfere with the diuretic action of mersalyl in dosages upto 50 or 120 times respectively those of BAL ,

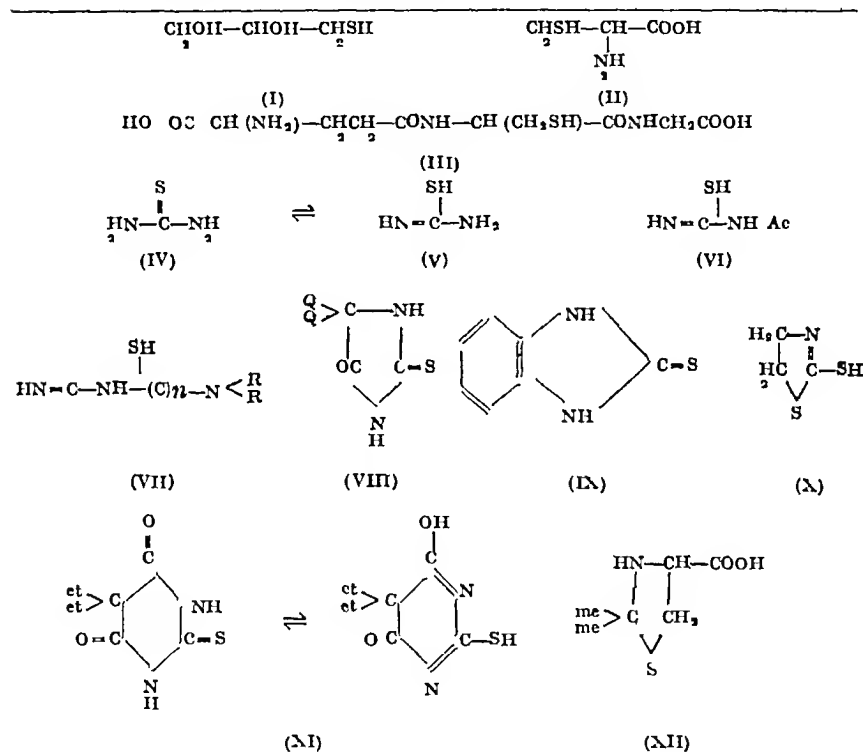
(3) That mersalyl when given intravenously produces severe cardiac toxic effect which can be prevented or abolished by the dithiol BAL as well as by monothiols, cysteine and glutathione, or thioglycolic acid

(4) They have further shown that contrary to dithiol BAL, the monothiols, cysteine and glutathione, in doses fully active against the cardiac effects, do not decrease urinary flow in the normal animal nor do they counteract the diuretic action of mersalyl

3 *In our recent investigations we have used the following thiol compounds in addition to BAL —*

- (1) Thiourca (IV)
 (2) 2—mercapto—4 1—diphenyl—5—Imidazolone (VIII) Thus 2—(5—Imidazolone) thiol has been abbreviated, as “Thiohydantamate—B” in the chart
 (3) Thiobenzimidazolone (IX) Named “Imidazolone” in the chart
 (4) 2—Thiozoline—2—thiol, (X)
 (5) 4—Hydroxy—5 5—diethyl—6—keto—5 6 dihydropyrimidine—2—thiol, (XI) Named “Thiobarbiturate—c” in the chart
 (6) 2—dimethyl—thiozolidine—4—carboxylic acid, (XII) Named “Thiozolidine—A” in the chart

TABLE 1



4 Method —All the experiments were carried out on dogs under paraldehyde anaesthesia, 2 c c per Kg body weight. In some of the experiments the chest was opened and artificial respiration carried on, while in others simple blood-pressure tracings were considered to be sufficient and so the chest was not opened and no artificial respiration carried on. The drugs in every case were injected directly into the femoral vein. A few preliminary experiments were repeated to ascertain the minimum lethal dose of Neptal for dogs, and it was found as in our previous communication (*loc cit*) that $3\frac{1}{2}$ m per kilo, of body weight was the M L D. We have selected three of these tracings to show the main results. See Figs I and II and III of the new drugs tried, on page 297.

TABLE II EXPERIMENTAL OBSERVATIONS

No	Wt of Dog	Details of Experiments	Quantity and Time of Administration	Effects	Results
1	8.2 Kilos	Normal blood pressure recorded chest opened & artificial respiration given	(a) Neptal 29 m ($3\frac{1}{4}$ m per Kilo) I/V followed by BAL 2 c c I/V. (b) After 10 minutes another injection of Neptal was given I/V (Same dose)	(a) There was no abnormality in the heart. No fall of B P. No fibrillations extra systoles. (b) No abnormalities were detected even at this time	Dog survived
2	6.9 Kilos	Normal B P recorded, chest not opened	(a) Neptal 25 m ($3\frac{1}{4}$ m per Kilo) given I/V quickly (b) 40 seconds after starting of irregularity BAL 2 c c was given I/V	(a) After one minute there was a marked fall in B P followed by irregular action of the heart. (b) The irregularity began to diminish till within 2 minutes B P became normal & the irregularity disappeared	Dog survived
3	10.0 Kilos	B P recorded, chest not opened	(a) Neptal 35 m ($3\frac{1}{4}$ m per Kilo) I/V quickly (b) 20 sec after the irregularity BAL 2 c c given I/V	(a) After 15 sec the heart became irregular with a marked fall in B P. (b) The irregularity began to diminish till within two minutes it became regular	Dog survived
4	8.5 Kilos	B P recorded, chest not opened	(a) Neptal 30 m ($3\frac{1}{4}$ m per Kilo) given I/V (b) 40 seconds after irregularity BAL 2 c c given I/V	(a) After 30 seconds there was marked fall in B P followed by irregular action of the heart. (b) The irregularity diminished and heart became regular within 2 minutes	Dog survived
5	8.2 Kilos	Normal B P recorded chest opened and artificial respiration given	(a) Neptal 33 m (4 m per Kilo) given I/V quickly (b) 30 seconds after irregularity 2 c c BAL given I/V quickly	(a) After 30 seconds there was a marked fall in B P and cardiac irregularity (b) No effect and dog died	Dog died
6	7.3 Kilos	B P recorded, chest opened	(a) Neptal 30 m (4 m per Kilo) given I/V quickly (b) Immediately after the irregularity BAL 2 c c given I/V	(a) After 17 sec heart became suddenly irregular (b) No effect	Dog died

No	W I of Dog	Details of Experiments	Quantity of time of Administration	Effects	Results
7	9 1 Kilos	B P recorded, Chest not opened	(a) Neptal 32 m (3½ m per Kilo) given I/V (b) Immediately Thiazolidine "A" 2 c c 2% given I/V	(a) After 10 sec there was a fall in B P (b) The blood pressure after falling became normal and dog survived	Dog survived
8	8 2 Kilos	B P recorded, Chest not opened	(a) Neptal 20 m (3¼ m per Kilo) given I/V quickly (b) 30 c c after irregularity 3 c c 2% Thiourea given I/V quickly	(a) After 20 seconds there was marked fall in B P followed by irregular action of heart (b) No effect and dog died	Dog died
9	7 6 Kilos	B P recorded, Chest not opened	(a) Neptal 26 5m (3¾m per Kilo) given I/V quickly (b) 30 c c after irregularity 4 c c 2% Thiourea given I/V quickly	(a) After 25 seconds there was a marked fall in B P followed by irregular action of heart (b) No effect and dog died	Dog died
10	8 2 Kilos	B P recorded, Chest not opened	(a) Neptal 20m (3¼m per Kilo) given I/V (b) 20 Seconds after irregularity Thiohydantonnate "B" 2% 2 c c given I/V	(a) After 20 seconds there was a marked fall in B P followed by irregular action of heart (b) No effect and dog died	Dog died
11	7 3 Kilos	B P recorded, Chest not opened	(a) Neptal 25m (3¾m per Kilo) given I/V (b) After 10 seconds of irregularity 2% 2 c c Imidazole given I/V	(a) After 10 seconds there was a marked fall in B P followed by irregular action of heart (b) No effect and dog died	Dog died
12	6 4 Kilos	B P recorded, Chest not opened	(a) Neptal 22m (3¼m per Kilo) given I/V (b) Immediately after irregularity 2% 2 c c Thiazoline-2 Thiol given I/V	(a) There was a marked fall in B P and heart became irregular (b) There was rise in B P but the irregularity contained and dog died after 5 minutes	Dog died
13	8 2 Kilos	B P recorded, Chest not opened	(a) Neptal 20m (3¼m per Kilo) given I/V (b) 10 Seconds after irregularity Thiobarbiturate "C" given I/V	(a) After 30 seconds there was a marked fall in B P followed by irregular action of heart (b) No effect and dog died	Dog died

Discussion —There is experimental and clinical evidence to show that sudden death may occur after intravenous injection of mercurial diuretics in a certain proportion of cases. Further, the experimental evidence points out that these reactions occur because of disturbances in the specific heart musculature resulting in ventricular fibrillation. Various attempts have been made from time to time to find out certain substances which, if added to the mercurial diuretics, could prevent fatal reactions in human beings. Pines et al (1949) have carried out experiments on dogs and come to the conclusion that magnesium sulphate has a suppressive effect upon the ventricular fibrillation produced by the administration of mercurial diuretics. They observed a very favourable action of 0.5 c.c. of a 20% solution of magnesium sulphate upon the course of the heart intoxication due to intracardiac or intravenous injection of Esidrone.

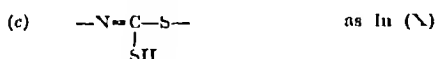
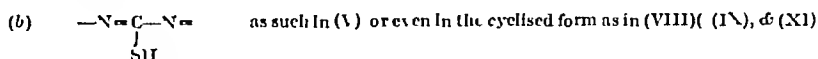
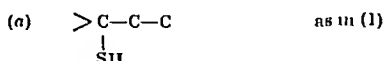
We repeated some of the experiments but did not find magnesium sulphate effective in preventing fibrillation after Neptal or Esidrone. On the other hand, we were convinced by our experiments that (loc cit) procaine hydrochloride, $\frac{1}{2}\%$, 1 c.c. prevents fibrillation caused by minimum lethal doses ($8\frac{1}{2}$ m. per kilo body weight) of Neptal when the injection was given slowly (2 minutes). Procaine does not prevent fibrillation, however, if the dose of Neptal is large.

Meanwhile the advent of BAL and other thiol compounds marked a new era in this direction. It has been shown by Long and Farah that cysteine, glutathione, and BAL markedly reduce the cardiac toxicity of mersalyl. Their findings have been confirmed by Lehman who used thioglycolic acid. Later, Farah and Maresh carried out their work in order to study the effect of these sulphhydryls on the diuretic action of mersalyl and to find whether abolition of cardiac toxicity can be obtained only at the expense of abolition of kidney action, and their results have already been formulated.

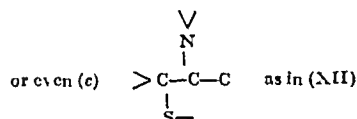
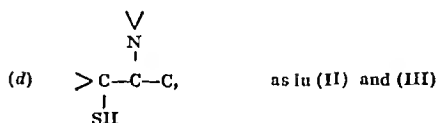
Our work also confirms that BAL markedly reduces the cardiac toxicity of Neptal. Thus, though BAL is an antidote to the mercurial diuretics in the sense that it prevents the fibrillation caused by I/V injection of Neptal, its great drawback is that it also neutralises the kidney action of the Neptal. Hence, *in actual practice*, it is not of much value *in therapeutics*, since the combination of BAL would defeat the very purpose for which Neptal is being given.

Besides, amongst the thiol compounds tested by us, "Thiozolidine—A" definitely checks the fibrillation produced by Neptal. In place of the monothiols, as 2-3-dihydroxy—propan—1—thiol, (I), which had been found to be ineffective, and the monothiol—carboxylic acids, as cysteine, (II), and glutathione, (III), which are weak antidotes in I/V Neptal poisoning, it was proposed to study thiourea, (IV), and its derivatives which in the tautomeric form (V) are known to possess a thiol structure and can react with metallic compounds. In case of its activity, its inherent toxicity was to be lowered by the introduction of short chains, (VI), or long dialkylaminoalkyl chains, VII. But thiourea was found to be inactive, and so its cyclic thiodiureides were tested, out of which only thiazoline—2—thiol, (X), could somewhat delay the onset of the toxic reaction. Next, it was thought desirable to try some cysteine derivatives, for cysteine was active. In view of the characteris-

the fission of thiozolidines with mercury compounds, this series was tried, the first compound of which, "thiozolidine—A" was found to be definitely effective in checking the fibrillation produced by Neptal. Further work is in progress. But we conclude that the thiol compounds containing the pharmacophores



seem to be inactive while those containing the pharmacophores



(which represents a sulphide linkage in place of the sulphadryl) are active, perhaps due to the anchoring action of the nitrogen atom on the neighbouring carbon in combating the toxicity of the I/V mercurial diuretics

CONCLUSION

1 BAL is effective in preventing the fibrillation caused by intravenous Neptal only if it is given immediately after the latter

2 2-Dimethylthiazolidine—Carboxylic acid also prevents the fibrillation caused by Neptal

REFERENCES

- 1 SWIFT H B and MALHOTRA C L. *The Indian Physician* 5 275 81, 1948
- 2 FARAH A and MARESH G. *Jour Pharmacol Exp Therapeut* 92, 73 82 1948
- 3 IGNACIO PINES ANTONIO SANABRIA and R T Hernandez Arriens. *British Heart Journal* 6, No 4 1944
- 4 LONG W K and FARAH, A. *Science* 104 220 1946 and *Jour Pharmacol Exp Therapeut* 88 388 1946
- 5 LEHMAN, R A. *Proc Soc Exper Biol and Med* 64 428 1947

Editor's Note —A mercurial diuretic with Sulphydryl radicle replacing theophylline is now put on the market by Campbell Products of New York under the name of THIOMERIN (Mercop tomerin) which is nontoxic and painless, and may be injected subcutaneously

KALA-AZAR: AN ENDEMIC FOCUS IN BOMBAY*

by

Y M BHENDE†, MD

N FIGUEREDO††, M B B S., B.Hy

N M PURANDARE†, MD

S L DESAI*†, M B B S

D D BANKER†, MD

In India, the geographic distribution of kala-azar, though extensive, is believed to be confined to the eastern side of the peninsula¹⁰ Here it extends in the north to the foot-hills of the Himalayas and in the south as far as Cape Camorin Bengal, Assam, Bihar, Orissa, and, Madras are the most heavily infected centres, in the first two provinces even epidemics have been noted In the United Provinces it occurs as far west as Lucknow and a few indigenous cases have been reported from Allahabad¹⁰ Outside these endemic zones a few asporadic cases have been seen in the Punjab, in the North West Frontier Province, on the west coast of India in the Madras Province, in Ceylon, and, in Burma, but, an indigenous origin for some of these places is doubtful or has been denied⁸ The nearest suspected (but as yet unproved) endemic focus to Bombay is Goa¹¹ Recently, a single proved indigenous case has been reported from Jaipur,⁴ and, last year, 2 such cases have been encountered in Lahore³ The distribution of kala-azar in India today, as compiled from the information available, is indicated by a map of India (Fig 1) It may be emphasised that for many of the places shown the incidence has been worked out not by systematic surveys but from the number of cases reported from those areas, this is specially so for most of the places *excluded* as non-endemic zones for kala-azar

Hitherto, both the province of Bombay and city proper have been considered "dry" areas for kala-azar and the few cases encountered locally from time to time have been classed as "imported", meaning thereby that the affected individuals had caught the infection outside in some endemic zone and had migrated to Bombay subsequently During the last 2 or 3 years, however, the feeling has grown that at least in some of these cases detected in Bombay the circumstances are such as to suggest an indigenous origin from a local source of infection Certainly many more such cases have been seen but, only 2 have been reported so far In both these cases the diagnosis was made by (1) demonstration of the Leishman-Donovan bodies in smears of the sternal marrow, and (2) growing the leptomonas from the marrow or the peripheral blood In the first case¹⁴ the patient was a resident of Bombay for 22 years and during that time the only outside place he had visited was Poona (a "dry" area about 120 miles from Bombay) In the second case¹³ the patient had resided in Bombay continuously for 18 years and the only outside place he had visited was Bassein (again a "dry" area about 40 miles from Bombay) Both these cases have been detected during the last 3 years

* A paper read at the 94th meeting of the Seth GS Medical College & KEM Hospital Staff Society, held on 9th July 1940

† From the Department of Pathology and Bacteriology, Gordhandas Sunderdas Medical College, Parol Bombay

†† From the Acworth Leper Home, Matunga Bombay

PLATT I

Swift et al —Sulphydryl Compounds

THE INDIAN PHYSICIAN—Oct 1949

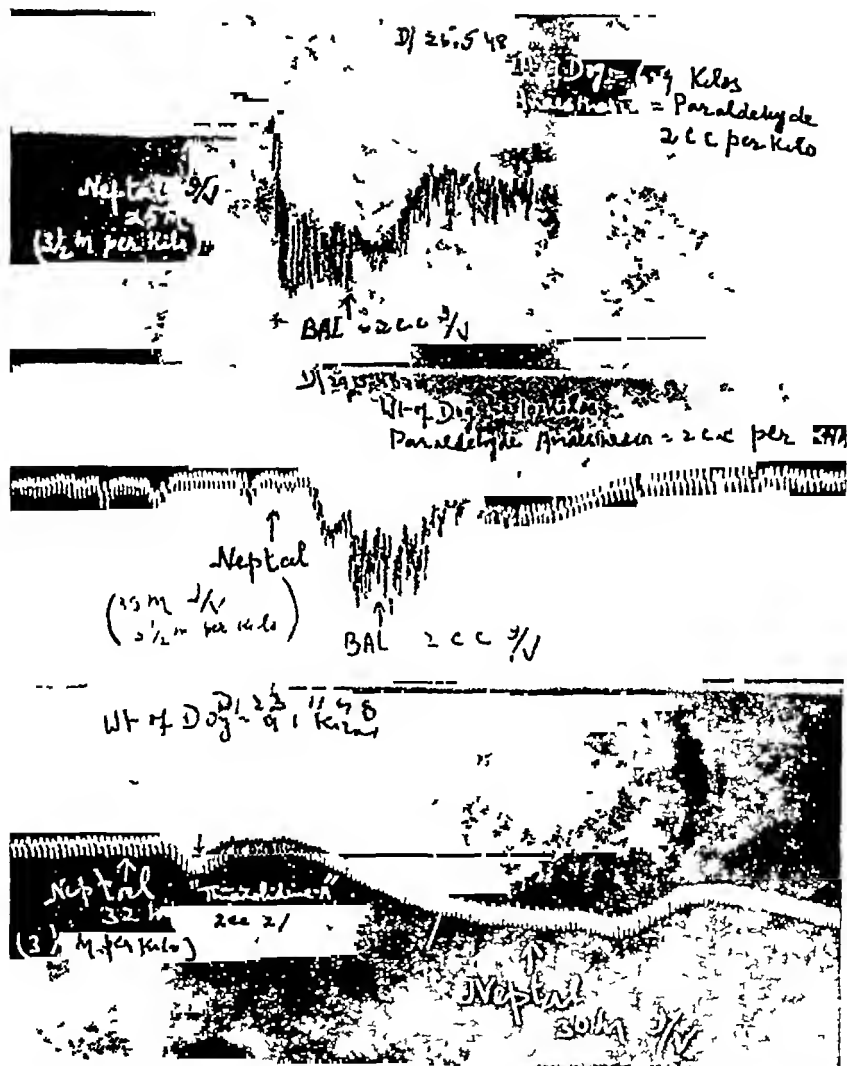


Fig —1—Exp observation No 2 (page 292)

Fig —2— No 3 (page 292)

Fig —3— No 7 (page 293)

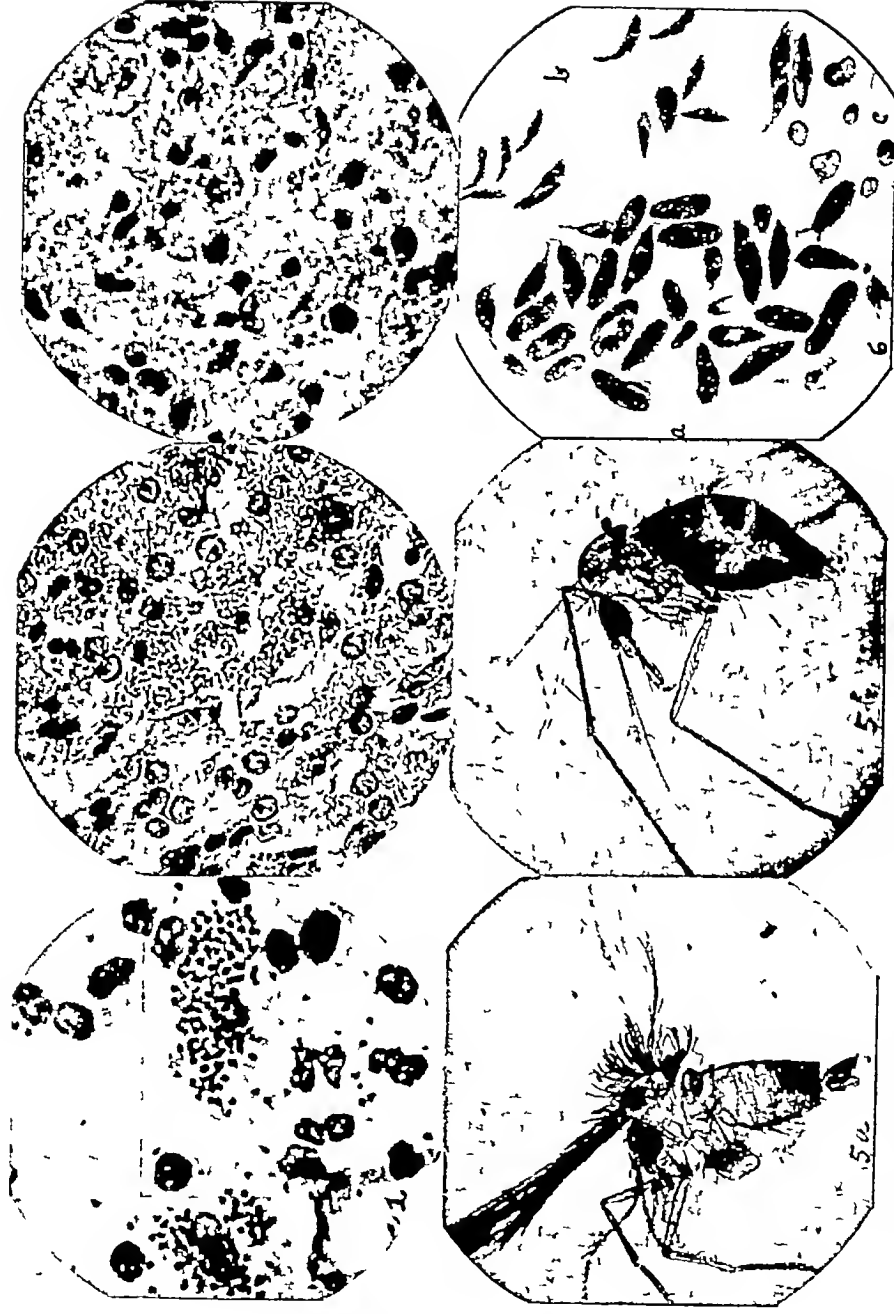


Fig. 2.—Smear of the Spleen from a fatal case. The Leishman-Donovan bodies are present in large numbers. Intracellular as well as extracellular forms can be made out. Giemsa ($\times 900$)

Fig. 3.—Section of the Liver from a fatal case. The Kupffer cells and the endothelial cells lining the sinusoids are packed with Leishman-Donovan bodies. H. E. ($\times 800$)

Fig. 4.—Section of the Spleen from a fatal case. The macrophage cells in the pulp are packed with Leishman-Donovan bodies. H. E. ($\times 800$)

Fig. 5.—The Sand fly. a male, b female. Note the hairy appearance of the long limbs and the characteristic venation of the wings. The male has elapser at the hind end. ($\times 100$)

Fig. 6.—A Composite Drawing prepared from several smears of crushed female sand flies. a and b: Leishman-Donovan bodies and flagellates c Leishman-Donovan bodies swollen and some with double nuclei (dividing forms). Giemsa ($\times 970$)

It may be granted, then, that there is strong but circumstantial evidence for the possible existence of an endemic focus of kala-azar in Bombay. A chance observation of one of us—to wit, the detection of 2 cases of kala-azar at autopsy during the course of a single week and in patients coming from the same source—gave us an opportunity to undertake a detailed investigation. We believe we have proved the existence of an endemic focus of kala-azar in Bombay. The results of our investigations were summarised in a preliminary communication.⁸ This paper gives the details of the work and presents the findings up-to-date.

1 *Outbreak of Kala-azar in a Local Institution*—Whenever possible all the bodies from the Acworth Leper Home, Bombay, are submitted for autopsy to the Department of Pathology and Bacteriology of the Gordhandas Sunderdas Medical College. From April 1948 to the end of May 1949, autopsy was performed on 22 such bodies. Of these, 11 patients were found to have suffered from kala-azar in addition to leprosy. The diagnosis of kala-azar was made by (1) demonstration of *L. donovani* in smears made from the spleen, and/or, (2) demonstration of the parasites in sections of the organs (mostly the liver and the spleen). Figure 2 shows the Leishman Donovan bodies in a smear made from the cut surface of the spleen and figures 3 and 4 illustrate the histopathologic findings in the liver and the spleen respectively. The histological sections of cases referred from the Acworth Leper Home prior to April 1948 were restudied but in the material up to January 1945 no more cases have been discovered. Material prior to this date is, of course, being scrutinised, however, we feel it unlikely that any cases will be found. The incidence of a series of 11 cases of kala-azar diagnosed at the autopsy in material coming from a single institution during a period of 14 months suggested the possibility of a localised outbreak. A further natural inference was that there must necessarily be among the present inmates of the Home some more cases of kala-azar. The Acworth Leper Home accommodates some 400 patients, and, though, it would have been ideal, it was not possible to investigate every patient by either a sternal marrow biopsy or a splenic puncture. The practical plan adopted was to collect the sternal marrow from any patient who had either (1) an enlarged spleen and/or (2) whose serum gave a positive Napier's aldehyde test. Up-to date 357 patients have been tested, and, 25 proved positive (13 strongly positive and 12 weakly positive *). Of these 25 patients, 16 were negative, 7 are still under investigation, and 2 have been shown to be suffering from kala-azar as shown by the presence of *L. donovani* in the smears of the sternal marrow and growth of the leptomonas in cultures on the N N N medium. Similarly out of 6 patients with splenomegaly 3 were proved to be cases of kala-azar.

Undoubtedly, due to the procedure we have adopted in our investigations, we must have missed some cases, especially the very early ones, as the aldehyde test first becomes positive 1 month after the onset of disease and is strongly positive only after 5 months.¹⁰ Nevertheless,

* The technique followed was that described by Napier.¹⁰ If the serum became solid and completely opaque within 15 minutes the test was considered as "strongly positive", if it became solid and completely opaque within 24 hours the test was considered "weakly positive". In the "negative" test the serum remains clear and solidification is of no significance.

the incidence of 16 cases of kala-azar in a single institution during a period of 14 months is by itself very suspicious of an indigenous origin. The case records of every positive case were analysed to determine (1) the place from which the patient came (2) the duration of his stay at the Leper Home, which could be taken to mean the duration of his stay in Bombay. Concerning this second point, above, it was found that the determination of duration of these patients' stay in Bombay proper from the total period of their segregation was misleading because many of them had absconded from the Home on one or more occasions and their movements outside could not be verified with certainty. The period of definite uninterrupted stay in Bombay was, therefore, calculated in each case from the date of the last re-admission to the date on which death occurred, or, up-to-date in the case of patients still alive. The data so obtained is shown in Table I. It will be



Fig 1 —Map of India showing the present distribution of Kala-azar

seen that 8 patients came from Madras (a proved endemic focus for kala-azar), 1 patient came from Goa (a suspected endemic focus), 2 from the Central Provinces and Berar, 2 from Bangalore, and, the rest 8 had their native places in the Bombay Province which so far has been considered a 'dry' area for kala-azar. It may be emphasized that these figures indicate the *minimum* duration of these patients' stay in Bombay. The exact range of the incubation period of kala-azar is not known, it is generally considered to be from 2 to 4 months¹⁰ and the widest range may be assumed to be anything from 10 days to 2 years¹⁹. When the figures for the minimum stay in Bombay are related to the incubation period it seems probable that many of our patients could have caught the infection in Bombay. And, in the case of at least 5 of them with a minimum of 3 years' uninterrupted stay in the Home (in one of these this was 13 years) we may safely presume that they were almost certainly infected locally. In our opinion these figures suggest very

strongly that the whole outbreak is of local origin and that it is not a chance accumulation of 'imported' material

2 *Presence of the Insect Vector (Sand-flies) in the Affected Locality*—Controversy still rages round the possible insect vectors of kala-azar, the bedbug, the fleas, the sand-flies and other blood-sucking diptera are main among those suspected¹⁹ Some have even suggested that the infection may occur by the oral or the conjunctival route¹⁹ The details may be read in the Reports of the Kala azar Commission, India^{5 & 6} Suffice it to say that the sand-fly is only insect-vector for which irrefutable evidence has been obtained The next step in our investigations was, therefore, to find out if sand-flies existed in the wards and the compound of the Acworth Leper Home There are no cattle sheds or live stock in the compound or in the vicinity of the Home, but, otherwise, the conditions necessary for the breeding of sand-flies are present¹⁰ By now we have trapped and examined some 983 "flies" of all kinds There was a large number of the members belonging to the family *Psychodidae*, these resemble the sand-flies but are not the insect-vectors for kala-azar Among our catch there are only 32 sand flies* [28 male, 9 female, (Fig 5)] This small number caught may partly be explained by their actual scarcity during the dry months (April, May and June) of the year, it may also be because of our method of trapping the flies** The pastime of catching the sand-flies is still going on and we may be able to catch them in larger numbers after the rain has cooled down the weather The insect-vector proved responsible for the transmission of kala-azar from one person to another is, therefore, present in the locality affected Sinton¹⁷ has given the geographic distribution of the various species of *Phlebotomus* known to occur in India As far as the Bombay Province is concerned four species are prevalent *P papatasi*, *P argentipes*, *P minutus* and *P minutus* var In the Bombay City proper, according to Sinton¹⁷ the prevalent species are *P argentipes*, *P papatasi* and *P minutus* Young and Chalam²⁴ have described two more species *P chalami* and *P colobaensis* Of these, *P argentipes* is undoubtedly concerned in the transmission of kala-azar nothing definite can be said about the others It is interesting to recall that in Bombay *P argentipes* was caught in a house at Marine Lines and in the municipal cow-sheds at Parel, Dadar and Byculla.²³ This was in 1924-27 and the distribution of sand-flies in Bombay at the present moment is not known

3 *Presence of Sand-flies Infected with L donovani*—The final step in our search for positive proof for the existence of an endemic focus of kala-azar in Bombay was to demonstrate the presence of female phlebotomus infected with *L donovani* With the exception of a few mounted as permanent specimens, every sand-fly was dissected and smears prepared from the material obtained by crushing the pharynx and the mid-gut The smears were stained with the Leishman or the Giemsa stain and searched meticulously for the parasites To date we have

* The identity was confirmed by Dr S R Rao, Parasitologist to the Government of Bombay to whom we are indebted for valuable help

** The 'flies' were caught by means of "light traps"—The glass of the hurricane lanterns was smeared with vaseline and the lanterns kept in wards, otherwise dark, all throughout the night. Four lanterns were kept in each of the wards for 7 days in succession

come across 4 infected female phlebotomi. Figure 6 is a composite drawing made from the positive smears. It will be seen that a variety of forms were seen. They are merely the various developmental stages of the parasite in the insect-vectors and the stage of development seen depends on the interval between the feed by the insect-vector on an infected person and the moment of its falling into the trap. We could identify altered Leishman-Donovan bodies as well as the leptomonas. Of the former nothing need be said, but about the latter we may add that morphologically they are identical with the leptomonas seen in cultures and those seen in sand-flies infected naturally and experimentally.¹⁵

DISCUSSION

Three factors are essential for the transmission of kala-azar: a primary source of infection, the transmitting agent, and a susceptible population. In the outbreak we have investigated the primary source could only be human.* When and how exactly was it introduced we are unable to say. We may point out, however, that 3 patients in this series came from Madras (see Table I), a highly infected endemic focus.

TABLE I

Serial No	Native Place	Date of 1st Admission	Date of the Last Re admission	Died on	Period of Uninterrupted stay in Bombay as calculated from the date of last re admission to date of death or up to 9-7-49		
					Years	Months	Days
1	Nasik Dist (Yeole)	7-3-46	7-10-47	Living	1	9	3
2	Satara Dist (Sakurda)	10-5-48	Never absconded	"	1	1	21
*3	Thana Dist (Uthan)	20-3-45	"	"	4	8	11
*4	Bangalore	21-6-44	8-2-45	"	5		19
*5	Ratnagiri (Savarda)	19-6-43	8-2-45	"	6	5	2
6	Madras	4-8-48	28-1-49	14-4-49		2	20
7	Madras	8-5-48	1-3-49	2-4-49		1	2
8	Madras	23-8-47	18-2-48	23-8-49	1	1	6
*9	Ratnagiri (Sangameshwar)	2-12-43	1-2-45	5-8-48	8	6	5
10	Ratnagiri (Malwan)	1-10-38	2-1-48	6-5-48		4	5
11	Kolaba Dist (Man good)	10-11-38	10-10-47	22-4-48		6	13
*12	Goa (Kolwal)	21-10-35	Never absconded	10-2-49	13	3	27
13	Ratnagiri (Raspatan)	13-10-45	29-9-48	1-3-49		5	
14	Bejar (Umratt)	4-3-48	8-12-48	4-3-49		2	25
15	Bangalore	25-5-48	17-5-49	28-5-49			12
16	Nagpur	2-10-43	28-3-49	27-5-49		2	

* Cases with more than 3 years uninterrupted stay in Bombay

for kala-azar. The sand-flies present locally caught the infection and succeeded in transmitting it to new hosts. In a community, susceptibility to any bacterial infection varies from individual to individual. The same holds true for kala-azar: not every person bitten by an infected sand-fly will develop kala-azar.⁷ This is mainly due to natural resistance. Undoubtedly in our patients the coincident leprosy must have lowered their resistance and facilitated the development of kala-azar, but, this decreased resistance (or increased susceptibility) could not

* A primary canine source may be discounted, so far only 2 cases of cutaneous Leishmaniasis in dogs have been reported in the whole of India and thousands of dogs have been examined in various places with negative results.¹

have been produced specifically by leprosy as such. This is evidenced by an experiment performed many years ago in which infected sand-flies were fed on lepers well looked after and in good general health, none of them contracted kala-azar.⁷ Further, to lower the general resistance any debilitating process is good enough, malaria^{3,21}, an influenzal epidemic²² and bad economic conditions²² have been shown to have rendered a large population susceptible to an epidemic outbreak of kala-azar. If the significance of the above arguments is grasped, it must be admitted that with a reservoir of kala-azar cases ready to serve as a primary source of infection and with the insect-vector present in the vicinity there is every chance of the infection spreading widely in the general population of this city, or, even further. That such spread has actually occurred from small lurking foci is evidenced by the reports of the indigenous cases^{13 & 14}. How quick and how far will be the spread will depend mainly on conditions favourable for the rapid breeding and transport of the insect-vector. Barring (1) absence of alluvial soil, (2) presence of heavy winds from the sea and perhaps (3) good sanitation, all the conditions thought favourable for the intermediate host are present in Bombay.⁹ How badly will the population suffer will to some extent be determined by its natural resistance. Lastly, it is well worth remembering that it is most difficult, if not impossible, to eradicate an established endemic focus of kala-azar.

It is hoped that our health authorities are alive to the danger of the situation. On our part we should keep in mind the possibility of kala-azar in any case of obscure pyrexia or splenomegaly.

SUMMARY AND CONCLUSIONS

1. A series of 16 cases of kala-azar encountered at the Acworth Leper Home during a period of 14 months is described.

2. Positive proof is adduced to show that the whole outbreak is of indigenous origin. This consists of (a) the long uninterrupted duration (more than 8 years) of some of these patients' stay in Bombay (b) demonstration of the presence of sand-flies in the vicinity (c) demonstration of the presence of infected sand-flies.

3. The danger of the spread of infection from the endemic focus to the general population of the city is pointed out.

REFERENCES

1. AVARI, C. R. and MACKIE, F. P. *Ind Med Gaz* 59 604 1924
2. BHENDE Y. M. PULANDARE, N. M. BANKER D. D., FIGUREDO N., and DESAI S. D. *Ind Physician* 8 111, 1940
3. CHAND A., GUPTA D. C., and CHUTTANI P. N. *Ind Med Gaz* 83 291 1943
4. HEILIG R. and NARAIN SACHDEV R. *Ind Med Gaz* 82 336 1947
5. *Indian Medical Research Memoir No. 4* Reports of the Kala azar Commission India Report No. I (1924-25) Thackers Spink & Co. Ltd. Calcutta 1926
6. *Indian Medical Research Memoir No. 25* Reports of the Kala azar Commission India Report No. II (1926-30) Thackers Spink & Co., Ltd. Calcutta 1932
7. KNOWLES R. Far Eastern Ass. Trop. Med. Trans. Seventh Congress British India Thackers Press and Directories Ltd. Calcutta Vol. III p. 1, 1927
8. NAPIER, L. E. quoted by 19
9. NAPIER L. E. Rep. Kala azar Comm. Rep. No. I *Ind Med Res Memoir No. 4* p. 219, 1926
10. NAPIER L. E. : *The Principles and Practice of Tropical Medicine* Thackers Spink & Co., Ltd., Calcutta 1st Ed. 1943
11. NAPIER L. E., and MUIR E., Kala azar Oxford University Press Humphrey Milford, 1st Ed. 1923

- 12 PATEL N D, Personal Communication
 - 13 RAOPATAN, P *Indian Physician*, 8 3, 1949
 - 14 ROW R and PATKAR, N A *Ind Physician* 6 251, 1947
 - 15 SHORTT H E, BARRAUD, P J, and CRAIGHEAD, A C *Ind Jour Med Res* 13 947, 1926
 - 16 SHORTT H E CRAIGHEAD, A C, and SWAMINATH C S *Ind Jour Med Res* 16 : 263 1928
 - 17 SINTON J A *Ind Jour Med Res* 14 941, 1927
 - 18 SMITH R O A HALDER, K C and AHMED, I *Ind Jour Med Res* 29 700 1941
 - 19 *Still's Diagnosis Prevention and Treatment of Tropical Diseases* The Blakiston Co, Philadelphia Vol I, 6th Ed, 1942
 - 20 SWAMINATH C S, SHORTT H E and ANDERSON, L A P *Ind Jour Med Res* 30 473, 1942
 - 21 TURKHUD D A, KRISHNAN, K V, and SEETHARAMA AYER P V *Ind Jour Med Res* 13 703 1926
 - 22 YOUNO, MACCOMBIE T C *Kala azar in Assam*, H K Lewis & Co, London 1st Ed 1924
 - 23 YOUNO, MACCOMBIE, T C *Ind Jour Med Res* 14 670, 1927
 - 24 YOUNO, MACCOMBIE T C and CHALAM B S *Ind Jour Med Res* 14 849, 1927
-

Critical Notes and Abstracts

MERCURIAL DIURETICS FOR CLINICAL USE

(1 ml of any of the following preparations contains 30 mg of mercury)

I MERSALYL	B P, U S P, SALYRGAN (Bayer)	Injection — I M painful, lump formation, necrosis I-V danger of vent fibrillation
II MERSALYL and THEOPHYLLINE	NEPTAL (M B), ESIDRONE (Ciba), SALYRGAN-THEOPHYL LINE, (Bayer), MERCUXANTHIN (MERC U PURIN) (Campbell), MERCUROPHYLLIN (Campbell)	I M less painful, lump formation I V danger of vent fibrillation
III MERALLURIDE SODIUM	MERCURHYDRINE (LAKESIDE LAB)	I M well tolerated I-V danger of vent fibrillation
IV MERCAPTOMERIN SODIUM	THIOMERIN [the disodium salt of N (gamma carboxy- methyl mercapto mercuri beth methoxy) propyl camp horamic acid] Theophyllin Complex in this preparation is replaced by mercaptide (Sulphydryl) group, (Camp bell Products)	Subcutaneous, very well tolerated, excellent diuretic response in 2 to 6 upto 12 hours or more Experimentally least toxic of all mercurial diuretics because of the sulphur radicle

EFFECTS OF SALICYLATES

During the course of the clinical evaluation of a new aspirin tablet containing aluminum hydroxide, Hoffman, Pomeranc, Volini and Nobe studied the effect of aspirin in high doses on the course of acute rheumatic fever and some of the biochemical changes that occur during its administration. Their report deals particularly with the findings in respect to sedimentation rate, prothrombin concentration and acid-base balance. Eighty adult patients with acute rheumatic fever were treated with aspirin until disappearance of clinical symptoms of the disease.

Of 65 patients started with control tablets of aspirin eight complained of gastric distress following ingestion. This distress disappeared when tablets containing aspirin and aluminum hydroxide were substituted. For most of the period of therapy in all patients, aspirin plus aluminum hydroxide was administered. Some symptoms of salicylism occurred in almost all patients when the plasma salicylate level was more than 30 mg per 100 c c.

Only 41 patients could be maintained at this level, 39 had to be given doses that produced levels under 25 mg per 100 c c. The sedimentation rate subsided to normal in a slightly larger proportion of patients in the group with high plasma salicylate levels. The prothrombin concentration was only slightly affected by aspirin therapy. A

drop below 75 per cent of normal occurred in one-third of the cases, there not being any difference in incidence in the high or moderate dose groups. A moderate fall in serum bicarbonate occurred in most cases, associated with an elevated serum chloride and a slightly diminished serum sodium. The blood pH was usually normal. The urine was usually acid.

It is believed that salicylate produces a primary hyperna with alkalosis but that the accumulated salicylate produces a fixed acid acidosis and that the two effects are mutually compensatory. The apparent salicylate clearance after aspirin therapy is only about 3 per cent of the creatinine clearance when the urine is highly acid. It increases three to eight times when the urine is alkalinized with sodium bicarbonate. Most of this increase is in free salicylate. Alkalinization is therefore of prime importance in the treatment of salicylate poisoning.

(Hoffman, William S. Chicago, Ill. Pomeroy, Mark Volini, Italo F. and Noble, Catherine. Treatment of Acute Rheumatic Fever with Aspirin. *The American Journal of Medicine* VI 433 April 1949.)

TREATMENT OF EARLY SYPHILIS WITH SMALL DOSES OF CRUDE PENICILLIN

The authors have recently completed a 34 months or longer continuous observation on a total of 109 of 159 patients with dark field—positive early syphilis who were treated by one of three intensive schedules, utilizing small amounts of penicillin alone or in combination with oxyphenarsine hydrochloride. In the first group, patients with early infectious syphilis were treated with 1,000 Oxford units of crude aqueous sodium penicillin every three hours for a total of 60 injections. Of these 31 patients, 72.7 per cent were considered to have had relapse while six patients, 27.3 per cent, who were treated with the small amount of penicillin alone, were clinically and serologically well for the duration of their post-treatment observation period.

In group two, 47 patients were treated with a similar dose of crude aqueous sodium penicillin and concomitantly 40 mg. of oxyphenarsine hydrochloride which was administered daily for a total of 320 mg., and 19, or 55.9 per cent, were considered to have had relapses while 15 or 44.1 per cent were clinically and serologically well for the duration of their post-treatment period.

In the third group, of the 31 patients treated with a total of 300,000 units of penicillin, 35, or 66 per cent were considered to have had relapses while 18 of the 31, or 34 per cent, were clinically and serologically well for the duration of their post-treatment observation period. Up to date, 109 patients, 80 percent with seronegative primary syphilis, 45 percent with seropositive primary syphilis and 27 percent with secondary syphilis were "Cured." Although only small doses of crude penicillin was administered in six patients with syphilis complicating pregnancy, five children observed over a long period were found to be free from the disease. The data substantiates the theory that with the low dosage, low unitage penicillin therapy demonstrated there may have been spirocheticidal components other than the penicillin in the crude mixture.

(Walker, A. E., and Utterback, Manly. Treatment of Early Syphilis with Small Doses of Crude Penicillin. *Archives of Dermatology and Syphilology* 59:277-283 March 1949.)

STEROID HORMONES

Investigation by Reiss of 12 hormones in relation to their fungistatic and genestatic effect on 14 pathogenic fungi revealed that no parallelism can be drawn between a specific physiologic effect and the fungistatic effect. The fungistatic effect apparently does not depend on the specific estrogenic or androgenic character of the investigated compounds, but probably depends largely on their molecular structure. It has been demonstrated that neither the androgenic nor the estrogenic compounds act in a uniform way indicating that these hormones are lacking their characteristic biologic activity. The estrogenic hormones exert a more appreciable genestatic action than androgenic hormones.

The most effective fungistatic compound is diethylstilbestrol. *Monilia albicans* and *Tortula histolytica* show an enhanced growth in steroid hormone-containing mediums. Because of the rather diverse observations, no final conclusion can be drawn as to what effect steroid hormones have on the infection in the human or animal host but the possibility that steroid hormones may effect the course of a mycotic infection directly, may alter the structure of the protein molecule in such a way as to make the growth unsuitable for a certain group of pathogenic fungi.

(Reiss, Fredrick, New York, N.Y. Steroid Hormones. *Archives of Dermatology & Syphilology* 59:405-413 April, 1949)

PRENATAL MATERNAL FACTORS IN MONGOLISM

The author presents a series of 64 pregnancies resulting in mongoloid children. Six cases were discarded as "without explanation." In 8 to 10 per cent satisfactory data could not be obtained, either because information was withheld or because only a thorough physical examination and clinical study could produce the necessary facts. Fifty cases were divided into four groups according to age. In the first age group, the mother was within or near the menopause. In 69 per cent she had not given birth to a child for a long time (seven to 16 years). Uterine and ovarian dysfunction and previous abortions indicate an impaired generative faculty which developed in a previously healthy woman who, in the majority of cases, had given birth to normal children previously.

Mongolism is not a "monstrosity", but the result of a deceleration of the development rate during certain weeks of the gestation period (end of organogenetic period, from the sixth to the 14th week). The result of such interference with the developmental rate is an immature, "ill finished" child.

Potentially, mongolism can be the outcome of any pregnancy, if a constellation of factors occurs which produces a threshold condition of sterility. The most frequent constellation of an abnormal pregnancy response is produced by advanced age. Of the women having a mongoloid child after 41 years of age, 53.9 per cent showed actual menopausal symptoms. Age produces a physiologically changed ovarian activity and uterine responsiveness. It is suggested that such a constellation facilitates the slowing down of fetal development due to abnormal nutrition.

Since 45 per cent of the instances of mongolism, however, occur in a maternal age group below 40 years of age, who are well fitted for procreation, age alone can not be the decisive factor. Analysis of 21 in-

stances in a maternal age group of 31 to 40 and of 18 instances in a maternal age group of 21 to 30 shows that certain constellations of factors may be expected to operate in all women who give birth to a mongoloid child in their twenties and thirties. The most significant symptoms are inability to become pregnant, impaired hormonal regulation, bleeding during pregnancy, menstrual irregularities, previous abortions and uterine and ovarian anomalies. These symptoms are the result either of local conditions in ovary and uterus or of an endocrine inadequacy of the corpus luteum.

Thyroid anomalies are so frequently seen that they are an important link in the chain of events. The common denominator is a threshold condition of sterility. The material includes one case with mongoloid children in two generations, one of multiple mongolism and three cases of twin pregnancies, resulting in one mongoloid, the twin being either normal or dead. It is pointed out that this material does not favor a genetic interpretation. It is, however, possible that thyroid deficiencies on either a geographic or a genetic basis are significant.

Mongolism, occurring about three times in every thousand births, is a condition which deserves more medical attention. As a "decelerating" growth deficiency in the prenatal period, still manifest in infancy, therapy has to concentrate on factors which may increase the developmental rate of the newborn. Although no definite cure is available, effective experimental treatment aiming at an increase of the growth rate (physical and mental) must start as early as possible.

The main problem of mongolism is its prevention. With increased knowledge of those prenatal factors operating during gestation and resulting in malformations or deficient growth rates, careful observations must be collected with regard to all circumstances which may condition abnormal fetal growth. The present study offers new evidence that mongolism is due to an abnormal maternal condition during the early part of gestation. It offers some clues as to the nature of the anomalies and postulates further investigations as to their specific mode of action.

(Benda, Clemens E. Waverly, Mass. Prenatal Maternal Factors in Mongolism. *Journal of the American Medical Association* 139:970-985 April 1949.)

CLINICAL EFFECTS OF LOBOTOMY

In a recent paper by Sands and Malamud, an intensive study of a series of cases of schizophrenia treated by prefrontal lobotomy is presented, in which the postoperative developments have been recorded in a series of rating scale determinations. It was shown that by use of a base line representing the psychological functions of the individual before the onset of his illness, the course of the disease could be evaluated in terms of his own normal personality characteristics rather than in terms of a theoretical normal for the population. The study covered 12 patients diagnosed as schizophrenia of the various subgroups. In all these patients adequate base lines were established on the basis of information from reliable sources reporting the qualities of their premorbid personalities.

The determination here reported were all made in relation to only one method of therapy, namely lobotomy. Although nearly all patients had received other forms of therapy previously, each was regarded by the hospital staff as suitable for lobotomy. All patients were males and

ranged in age from 19 to 37. The duration of the psychosis before lobotomy was two years to six years, four months. Rating scale evaluations were done twice before operation and every two weeks thereafter for a minimum of four months. Final ratings were done on all 12 patients at an average time interval of $7\frac{1}{2}$ months postoperatively.

In the series, it was seen that a significant number of patients were more aggressive and openly belligerent following lobotomy, and those patients who were selfdeprecatory or self-mutilative have become less so. A remarkable shift from an intrapunitive type of aggressive behavior to an extrapunitive one was seen. This reversal of the schizophrenic process in some cases seriously impairs the patient's chances for social adjustment. It is shown that the rating scale enables one to evaluate the effects of a given method of therapy in two different but highly important areas: (a) upon symptoms produced by the disease itself, and (b) upon personality functions not necessarily involved in the disease process. The clinical psychiatrist can better determine the quantity as well as the quality of the changes occurring in the course of disease and as a result of therapy.

(Sands, Sidney L. Worcester, Mass. and Mahmud, William A. Rating Scale Analysis of the Clinical Effects of Lobotomy. *The American Journal of Psychiatry* 105:700 April 1949.)

CARDIOVASCULAR REJECTEES

A follow-up study, made in 1947, of cardiovascular rejectees is reported by White and his colleagues. The study was made by special cardiovascular boards in Boston, Chicago, New York, Philadelphia and San Francisco of 803 young men who had been originally rejected for military service because of diagnoses of cardiovascular diseases, hypertension or neurocirculatory asthenia, but later resubmitted as 1A in 1943 after examination by these same special cardiovascular boards. Certain problems are reviewed in the light of this re-examination.

Heart murmurs were the commonest cause for the original rejections, but their appraisal by the cardiologists was not considered difficult. The great majority of the murmurs were variable, unimportant and physiologic in type, being heard in at least half of these young men. In four men rheumatic heart disease developed during the four years. The most difficult problem was that of the appraisal of slight elevations of blood pressure, in particular of transient hypertension (over 150 mm systolic or over 90 mm diastolic, subsiding after one-half hour's rest). Of 67 men showing transient hypertension in 1943, 33 showed normal pressure readings in 1947, 17 still showed transient hypertension, and 17 had sustained hypertension had developed. Of 35 with transient tachycardia in 1943 (heart rate over 100 subsiding after one half hour's rest), 19 showed no tachycardia in 1947. In a few cases the reverse was true.

Another study has shown that transient hypertension and transient tachycardia are of about equal prognostic importance with regard to the later development of sustained hypertension. Heart size as measured by teleroentgenograms showed only minor variations, up or down, between the examinations in 1943 and those in 1947. In only four men did definite enlargement of the heart develop. Electrocardiography also presented little difficulty. There were a few borderline cases noted on both occasions, but only one showed a distinct abnormality at the end of the four years.

Neurocirculatory asthenia was an uncommon development over the four year period—there were seven men whose condition were so diagnosed in 1947 who were considered to be normal in 1943. Valvular lesions indicating rheumatic heart disease, not evident in 1943, were noted in four men in 1947. Many others gave a history of rheumatic fever in childhood or early adult life, but showed no sequelae. In general, the 303 men served long and well in the armed forces, even though a few were discharged for cardiovascular reasons and, like others of the group with noncardiac disorders, are now under the jurisdiction of the Veterans Administration.

Eight of the 447 original objectees who were accepted for services were killed in action. In the group with a history of rheumatic fever in early childhood or early adult life, recurrence of activity between 1948 and 1947 was distinctly uncommon, even in those who saw active war service. In almost all, rheumatic fever had occurred at least five years before induction. Valvular lesions indicating heart disease, not evident in 1943, were noted in only four men in 1947.

(White Paul D. Boston Mass., *et al*. Cardiovascular Rejection: A Follow Up Study. *Journal of the American Medical Association* 139 1049 1053 April, 1949.)

RUPTURE OF THE CHOROID

In a recently published article, Tower presented a review of the literature of traumatic choroiditis and a report of ten cases. It has been estimated by Roemer that rupture of the choroid occurs at a rate of about one per thousand patients with ophthalmic disorders. Any theory based on the assumption that an actual break occurs within the choroid, and that the lesion results directly from contrecoup, will have to account for a consistent, peculiar finding, namely, that a blow inflicted on the anterior segment of the eye may lead to trauma distal to the point of impact in only one of the three tunics of the fundus, even though the choroid situated between the retina and the sclera is in close contact with these other structures.

It is, therefore, hardly surprising that the causation of choroidal rupture is a highly controversial subject. In summarizing recent observations, the author stated that conceivably, an indirect injury to the eye may affect those efferent nerves which control growth and nourishment. Inhibition of the essential functions of a trophic nerve will result in necrosis of the tissue normally supplied by it. The important change is within the vessel wall, caused by traumatic disturbance of ocular innervation. Primary spasm increases permeability, and secondary dilatation accelerates the escape of blood into the tissues.

The characteristic finding of hypotony following contusion of the eyeball suggests interference with the balance of regional secretions, due to an innervational disturbance. In five of the ten cases reported by Tower, the lesion in the fundus was more or less crescent shaped, while the patterns in the remaining five cases were atypical, ranging from a small, irregular pigmented spot to a large, maplike area of choroidal destruction. These cases are representative of the various forms in which lesions of the vascular coat are encountered after non-penetrating trauma to the eyeball. In case one, a negro woman aged 29, the vision was 20/200, unimproved with correction. An unusually extensive lesion of the choroid was observed in the temporal region of the fundus, and involving the macular area. A search of the literature revealed no arcuate rupture of the choroid as large as the one reported.

Except for the differences in shape and position, all lesions presented similar characteristics. Necrosis and atrophy of the choroid were encountered in all instances. No essential dissimilarity could be detected which would have warranted a distinction between typical, i.e., arcuate and concentric, and atypical morbid changes on any basis other than the obvious discrepancy in shape and position.

A more precise terminology was proposed, arciform traumatic choroditis was considered a better name for lesions of concentric shape, and diffuse traumatic chroditis, for those of irregular outline.

(Tower, Paul M.D. Los Angeles Calif.: Traumatic Choroiditis. *Archives of Ophthalmology*, Vol. 41 341 March, 1919. Roemer, P. *Textbook of Ophthalmology* New York, Reiman Co., 1917, p. 837.)

GRANULOMA OF THE SKIN AT SITE OF INJURY BY A FLUORESCENT BULB

Because of the increased use of fluorescent lighting in homes and places of employment, lacerations caused by broken fluorescent bulbs may result in cutaneous lesion which are histologically similar to Boeck's sarcoid. The physician must be on guard and the development of nodules and ulceration at the site of lacerations caused by such fluorescent bulbs should arouse suspicion of granuloma due to beryllium. Report of a case over a two year period demonstrated the danger of careless disposition of burned out fluorescent bulbs. Suspicious lesions must be widely excised and subjected to careful histologic examination in order to eliminate the danger of recurrence of the granuloma.

(Coakley, Walter A. Brooklyn N.Y. et al. Granuloma of the Skin at Site of Injury by a Fluorescent Bulb. *Journal of the American Medical Association* 139 1147-1148 April, 1940.)

Reflections and Aphorisms

THE ABUSE OF THE ELECTROCARDIOGRAPH

“Instruments of precision in good hands can do good work, but in careless hands they have wrought havoc. This truth, directed to the electrocardiograph, has a particularly poignant meaning in that, material it can spoil is human and not inanimate. An uninformed observer with an electrocardiograph can more easily despoil lives than a reckless car driver on a busy highway. On this account it would seem as reasonable to insist on a proficiency test for the electrocardiographist as a driving test for the owner of an automobile. To know how to read an electrocardiogram should be a prerequisite to possessing an electrocardiograph in days when the machine is easily procurable and the demand for its services by a health-conscious laity daily increasing. In keeping with this was the visit of a patient the other day “to see how his T wave was going on.” The insistence of the test, however, is a fault more common to doctors than to patients. Examples of this travesty of its use abound, and one such was the demand that the electrocardiograph should accompany the consultant visiting a patient whose activities were said to be retarded and whose ankles had been swollen from heart failure, but in whom a superficial clinical examination made it clear that the former was the result of paralysis agitans and the latter was the outcome of a severe anaemia, a *non-cardiographic* examination showed that the heart was healthy. Another time came a confession from a doctor that the chief purpose of the consultation had been born of a desire to see at work a newer kind of direct writing electrocardiograph!

The advantages of a properly recorded electrocardiogram need not be extolled, for the test has proved its worth, but the warning bears repetition that the fallacies connected with it should be understood fully, and that its irregularities must be considered at all times alongside the symptomatology and physical signs elicited during a clinical examination of the patient. The electrocardiograph is meant to serve the clinician in his search for signs of an injury to the heart, it will do this unerringly only so long as it is used judiciously and by someone who can read its writing”—EVANS

CLINICAL PATHOLOGIST AND PRACTISING PHYSICIAN

“Clinical pathology is the laboratory analysis of symptoms and signs, and laboratory control of therapy. The method of the clinical pathologist is laboratory method, and leaves no room for misconception of him as an amateur physician. Yet his work demands considerable clinical training.

It is difficult for the untrained to appreciate fully that the interpretation of laboratory result is intimately associated with the techniques used to obtain them. And it is the acquisition of these techniques as his primary tools which distinguishes the pathologist from the physician. The question is one of orientation. The patient can only gain when the clinical pathologist thinks of *oedema* in terms of *plasma-proteins*, he can only lose if the physician fails to think in terms of *malnutrition*. Yet both think of *oedema*. Does this ban laboratory methods to the physician? By no means. The physician must have some training in clinical pathology. But the physician who habitually looks down the microscope [or in the test tube] is in grave danger of losing sight of his patient”—J FIELDING

The Indian Physician

VOL VIII NO II

NOVEMBER 1949

WHOLE NO 95

Original Contributions

AURICULAR FIBRILLATION

A STATISTICAL STUDY OF 102 CASES

AT

THE K E M HOSPITAL, BOMBAY

(From a total medical population of 30,104 patients)

by

RUSTOM JAL VAKIL, MD (Lond) M R C P (Lond)

(From the Cardiological Department K. E. M. Hospital
BOMBAY)

Auricular fibrillation (or "delirium cordis" or "pulses irregularis perpetuus" or "absolute or perpetual arrhythmia" or "mitral pulse") has been known to clinicians for years, especially as a frequent complication of advanced rheumatic heart disease

From the time of MacWilliam's original observation of auricular fibrillation in animals, in 1887, much has been added to our knowledge of the subject by the pioneer observations and investigations of Cushny (1899), Roltiberger and Winterberg (1909), Thomas Lewis (1909-1910), Jolly and Ritchie (1910-1911) and many others

Clinically, Auricular Fibrillation manifests itself by a complete or total irregularity of the rhythm of the heart and pulse, this is accompanied in the majority of cases, by an undue rapidity of heart action

According to Cowan and Ritchie (1935), "Auricular fibrillation is one of the most frequent disorders of the heart in persons over 20 years of age" In Paul White's opinion (1946), "Auricular fibrillation", one of the commonest, most interesting, and most important disorders of cardiac rhythm, ranks "probably third in frequency as a disturbance of rhythm, premature beats and paroxysmal auricular tachycardia ranking first and second" According to George Hermann (1940) "Auricular fibrillation constitutes about 50 per cent of the cases of persistent arrhythmia of the human heart"

Of 3,000 cases, with cardiac symptoms of signs, analyzed in New England by White and Jones (1928), 12.5% or 376 cases displayed Auricular fibrillation, of these, 82.2% or 309 cases had persistent or permanent fibrillation and 17.8% or 67 cases had paroxysmal fibrillation. The incidence of persistent auricular fibrillation, in these series, worked out at 10.3% of cardiac cases

Selection and Nature of Material

During the five year period, from 1941 to 1945 (inclusive) 30,104 patients (75.5% males and 24.5% females) were admitted as medical in patients at the K E M hospital, Bombay. Of these, 1860 cases (78.2% males and 21.8% females) belonged to the category of Cardiovascular disease. These cardiac cases have already been analyzed, in detail, from the aetiological stand point, in accordance with the report of the Criteria Committee of the American Heart Association.

Results of Investigations

The Incidence of Auricular Fibrillation — After a careful survey of our case-records we could collect a series of 102 cases of the so called "persistent" or "permanent" or "established" form of auricular fibrillation. Cases of paroxysmal auricular fibrillation being transient or brief, seldom seek admission into hospitals in India, and hence cases of this variety of fibrillation have been rigidly excluded from the discussion.

The incidence of Auricular Fibrillation, in our series, therefore, works out at 5.5% of all cardiac patients and 0.84% of all medical in-patients. In other words, about one case in every eighteen of heart disease and about one case in every 294 medical cases admitted to hospital, displayed auricular fibrillation.

The incidence of fibrillation in our series is therefore about half of that observed by White and Jones (1928) viz 10.8%.

There were only 4 cases of Auricular Flutter observed in our series of cases (1860 cardiacs) i.e. an incidence of only about 0.21%.

The ratio of fibrillation to flutter cases in our series works out 25.5 to 1. In the opinion of Cowan and Ritchie (1935), the corresponding ratio has been 15 to 1. In Paul White's opinion, Auricular flutter is diagnosed "only about twice to every fifty cases of auricular fibrillation," in the absence of graphic records. With routine electrocardiographic studies, however, the ratio of fibrillation of flutter cases works out at about 14 to 1 (White, 1946).

The Aetiological Relationships of Auricular Fibrillation

Since the time of Cabot (1914), who inaugurated a new era in scientific medicine by his aetiological approach to the classification of diseases of the heart, much has been said and written on the Aetiological Incidence of Cardiovascular diseases. The matter has lately been put on a scientific foundation by the laudable efforts of the Criteria Committee of the American Heart Association.

The Aetiological Incidence of Auricular Fibrillation has been worked out by many authorities.

In White and Jones' (1928) series of 346 cases of Auricular fibrillation with organic heart disease, the aetiological grouping was as follows — Rheumatic heart disease 45.6% (158 cases), Coronary heart disease 21.4% (74 cases), Hypertension (uncomplicated) 4.3% (15 cases), Hypertension (complicated) 26.6% (92 cases) and Thyrotoxicosis 4% (14 cases).

In an analysis of 575 consecutive cases of auricular fibrillation, reported by McEachern and Baker (1932), the aetiological grouping was reported as follows — Rheumatic heart disease 34.4%, Coronary

disease and old age 31.1%, Hypertension 16.9%, Thyrotoxicosis 7.5%, Emphysema 5%, Syphilis 3% and Miscellaneous cases 2.1%

In Cowan and Ritchie's (1935) series of 500 cases, 175 cases were rheumatic, 33 Thyrotoxic, 20 Syphilitic and 272 elderly Arteriosclerotic.

The Aetiological Grouping of cases of auricular fibrillation, in our series, was as follows —

1	Rheumatic Heart Disease	38 cases	37.3%
2	Syphilitic " "	2 " "	2.0%
3	Bacterial " "	1 case	1.0%
4	Hypertensive " "	14 cases	13.8%
5	Coronary " "	5 " "	4.9%
6	Pulmonary " "	7 " "	6.3%
7	Thyrotoxic " "	9 " "	8.8%
8	Senile or old Age " "	7 " "	6.9%
9	Cholecystitis " "	1 case	1.0%
10	Pneumonia " "	1 " "	1.0%
11	Extraneous Factors " "	2 cases	2.0%
12	Of obscure origin " "	15 " "	14.6%

The great importance of Rheumatic Heart Disease in the initiation of Auricular Fibrillation has been commented on by most writers on the subject. The percentage of incidence of Rheumatic factor, in cases of auricular fibrillation, has been reported differently by different authors viz, 69% by Cootson, 34.4% by McEachern and Baker, 48% by Stroud, Laplace and Reisinger, 35% by Cowen and Ritchie, 40% and 23.6% by Wedd and Mullins, 45.6% by White and Jones, and 66% by Hermann.

In our series of cases, the incidence of the Rheumatic factor was 37.3% (*i.e.* in more than one-third of all cases).

Only 4% of cases of fibrillation in Cowan and Ritchie's series of 500 cases and 8% in McEachern and Baker's series of 575 cases were of Syphilitic origin.

In Hermann's opinion, "bacterial endocarditis and auricular fibrillation are rarely associated." In our series only one case of auricular fibrillation was noted in the course of subacute bacterial endocarditis.

The "combination of auricular fibrillation and angina pectoris is extremely rare" (Hermann). From this point of view, it is interesting to note that 2% (or 2 cases) of our cases of auricular fibrillation also displayed angina pectoris.

6.9% or 7 of our cases of fibrillation were secondary to chronic Pulmonary Heart Disease of Chronic Cor Pulmonale. In all these cases, emphysema was associated.

The incidence of Thyrotoxicosis in auricular fibrillation has been reported as 7.5% by McEachern and Baker (1932), as 4% by White and Jones (1928) and as 6.6% by Cowan and Ritchie (1935). In our series, the incidence, works out at 8.8%.

It is generally accepted, nowadays, that a fairly small percentage of cases of auricular fibrillation is secondary to arteriosclerotic degeneration or to old age or to both. The extraordinarily high incidence of 'senile arteriosclerosis', viz 54.4%, reported in 500 cases of auricular fibrillation, by Cowan and Ritchie (1935), has not been confirmed by other authors. In our series, about 26 cases (*i.e.*, 25.5%) of

auricular fibrillation were secondary to hypertension, coronary disease, old age or arteriosclerosis

Of the 2 cases, in our series, secondary to extraneous factors, one was secondary to accidental poisoning from methylsalseylate and the other to electrical shock

The ratio of rheumatic to syphilitic cases, in our series, works out at about 19 to 1

TABLE I

THE INCIDENCE OF AURICULAR FIBRILLATION IN DIFFERENT AETIOLOGICAL GROUPS OF HEART DISEASE

Aetiological Group		No of Heart Cases	No of cases of A Fibrillation	Percentage Incidence
1	Congenital group	19	0	0 0
2	Rheumatic	461	38	8 2
3	Syphilitic	240	2	0 8
4	Bacterial	20	1	5 0
5	Hypertensive	500	14	2 8
6	Coronary	250	5	2 0
7	Pulmonary	186	7	3 8
8	Miscellaneous & unknown	317	35	11 0
All groups		1,860	102	5 5

It is interesting to note (Table No 1) that the highest incidence of auricular fibrillation was recorded in the so-called "Miscellaneous and unknown" group which includes, amongst other conditions, Thyrotoxicosis, Senility, toxic conditions etc

Excluding this heterogenous group, the incidence is highest in the Rheumatic group (8 2%) and in the Bacterial group (5%) The relatively lower incidence in the Syphilitic group (0 8%), the Hypertensive (2 8%) and the Coronary groups (2%) should be noted

Taking the three major infections of the heart *viz* rheumatic, syphilitic and bacterial, jointly into account, the incidence of fibrillation works out at 5 7% (or 41 cases out of 721)

Taking high-blood pressure, arterial disease and old-age, jointly into account, the incidence of fibrillation works out at about 3 3%

Sex Distribution—The sexes are not equally affected, in the case of auricular fibrillation Of the 500 cases of fibrillation studied by Cowan and Ritchie (1935), 284 (or 56 8%) were males and 216 (or 43 2%) were females

In a recent analyses of 645 cases of fibrillation at the Massachusetts General Hospital, the ratio of males to females was 71% to 29% (P White, 1946)

In our series of 102 cases, 75 (or 73 5%) were males and 27 (or 26 5%) females, the male to females ratio being 3 to 1

Age Incidence—According to Cowan and Ritchie (1935), the age-incidence of auricular fibrillation shows a steady rise from decade to decade, attaining its maximum "peak" in the seventh decade in males and the fifth and sixth decades in females McEachern and Baker (1932) from a study of 575 cases of auricular fibrillation, report the age-grouping as follows —Under 10 years of age, 0 5%, from 10 to 20 years, 4 2%, from 20 to 30 years, 5 4%, from 30 to 40 years, 15%, from

40 to 50 years, 20.2%, from 50 to 60 years, 26.1%, from 60 to 70 years, 20.5%, from 70 to 80 years, 7.8%, from 80 to 90 years, 0.8%

According to White (1946), the condition is very rare in infancy and early childhood and uncommon in adolescence

In our series of 102 cases of Auricular Fibrillation (inclusive of all aetiological types), the age-grouping was as follows —

Under the age of 10 years	No cases	0.0%
From 10 to 19 years	7 cases	6.9%
" 20 to 29 "	7 "	6.9%
" 30 to 39 "	26 "	25.5%
" 40 to 49 "	32 "	31.4%
" 50 to 59 "	19 "	18.7%
" 60 to 69 "	8 "	7.9%
" 70 to 79 "	2 "	2.0%
" 80 to 89 "	No case	0.0%
" 90 to 100 "	1 "	1.0%

The highest incidence was noted in the fifth decade of life (31.4%), which claimed almost one third of all the cases 75.6% or (three-quarters) of our cases were from 30 to 59 years of age and only 10.9% over the age of 60 years 6.9% of cases were below the age of 20 years and 18.8% were under 30 years of age

The youngest was a boy aged 10 years (rheumatic) and the oldest a man of 100 years old (senile)

The average age for the whole series worked out at 43.5 years

Age and Sex Incidence—This has been worked out in Table II. It will be observed that in both the sexes, the highest incidence is reached in the fifth decade of life, after which there is a definite drop

In the case of males, 11.9% of cases were over the age of 60 years, the corresponding for females was 7.4% 3.9% of males were over the age of 70 years, no females were reported over 70 years of age. On the whole, the age-incidence was more or less parallel for the two sexes

TABLE II

The Age and Sex Incidence of Cases of Auricular Fibrillation (102) cases

Age-Group	Males		Females	
	Number	Percentage	Number	Percentage
0 to 9 years	0	0.0	0	0.0
10 to 19 "	5	6.6	2	7.4
20 to 29 "	5	6.6	2	7.4
30 to 39 "	19	24.4	11	23.9
40 to 49 "	23	29.3	9	23.2
50 to 59 "	14	17.7	5	12.5
60 to 69 "	0	0.0	2	4.9
70 to 79 "	2	2.6	0	0.0
80 to 89 "	0	0.0	0	0.0
90 to 100 "	1	1.3	0	0.0
All age groups	75	73.5	47	45.7

The Ratio of Males to Females in Different Age-Groups—In 102 cases into consideration, 73.5 were males and 26.5% females

In cases below 30 years of age there were 71.4% males and 28.6% females. In cases from 30 to 59 years of age, the ratio was 27.8% males and 72.2% females and in cases over 60 years of age, it was 11.9% males and 88.1% females

to 18.2% females. In other words, the relative preponderance of males was more noticeable in the elderly age-groups.

Prognosis—Of the 102 cases of Auricular Fibrillation (all types), 26 cases proved fatal.

The death-rate, for the series, therefore worked out at 25.5%.

Auricular Fibrillation (Rheumatic)—According to Paul White (1946) auricular fibrillation complicates about one-fifth of all cases of chronic rheumatic heart disease. In White and Jones' (1928) series of 956 cases of rheumatic heart cases, auricular fibrillation was reported on 17.5%. It is said to occur in about two-thirds of cases of "severe" mitral stenosis (White 1946).

Incidence—In our series of 461 cases of rheumatic heart disease, auricular fibrillation (persistent form) was noted in 38 cases, giving a percentage incidence of 8.2%. This is less than half that reported by White and Jones (1928).

Age Distribution—Our youngest patient was a male aged 10 years and the oldest a male aged 56 years. The average age for Rheumatic fibrillation cases worked out at 38.6 years.

The age-grouping of our 38 cases of Rheumatic Auricular Fibrillation was as follows—

Under 10 years of age	No cases	0.0%
„ 10 to 19 years	7 „	18.0%
„ 20 to 29 „	4 „	10.5%
„ 30 to 39 „	14 „	37.0%
„ 40 to 49 „	10 „	26.5%
„ 50 to 59 „	8 „	8.0%
„ 60 to 69 „	No „	0.0%
Over the age of 70 years	No „	0.0%

It will be observed that the "peak" of incidence is reached in the fourth decade (37% of cases being in that decade), the "peak" for all rheumatic heart cases is reached in the third decade of life and for Chorea cases in the second decade.

Whilst 66% of our rheumatic heart cases were under the age of 30 years, only 28.5% of the auricular fibrillation cases were under that age. Whilst only 10.4% of rheumatic heart cases were over the age of 40 years, 34.5% of fibrillation cases were over that age.

In other words, auricular fibrillation selects the older age-groups (of rheumatic patients) by preference.

Sex Distribution—Out of 38 cases, 24 were males and 14 females, giving a ratio of 63.2% males to 36.8% females. The corresponding ratio for all "rheumatic heart cases" was practically the same (*viz* 65% males to 35% females).

Age and Sex Incidence—The ratio of males to females in the different age-groups, was as follows—

From 10 to 19 years	71.4% males to 28.6% females
„ 20 to 29 „	75.0% „ 25.0% females
„ 30 to 39 „	71.4% „ 28.6% „
„ 40 to 49 „	80.0% „ 20.0% „
„ 50 to 59 „	68.6% „ 31.3% females

There is a preponderance of males in all decades of life. The relative proportion of males was highest in the fifth decade of life (80%) and lowest in cases over the age of 50 years (66.6%).

Incidence of Structural Lesions (See Table No 3)—The most striking features of Table No 3 are the high incidence of mitral stenosis in the auricular fibrillation group (incidence of 47.4% or almost half the cases) and the low incidence of mitral regurgitation (0%). In the case of rheumatic heart disease group, the corresponding percentages are 13.1% and 10% respectively. Mitral insufficiency per se does not appear to be a cause of auricular fibrillation. Whilst the incidence of "double mitral disease" was about the same as that of "per se mitral stenosis" in the case of the fibrillation group (16 cases and 18 cases respectively), the former lesion was over three times as frequent as the latter in the case of rheumatic group (208 cases and 60 cases respectively). The low incidence of aortic valve disease (2 cases or 5.2%) in the auricular fibrillation group should be noted, the corresponding percentage for the rheumatic group was 9.1%.

TABLE III

Percentage Incidence of structural Lesions in cases of Auricular Fibrillation (Rheumatic) compared with corresponding figures for all rheumatic heart cases

Lesion	Auricular Fibrillation % incidence	Rheumatic cases % incidence
Mitral Stenosis & Insufficiency	45.0	45.2
Mitral Stenosis (pure)	47.4	13.1
Mitral Insufficiency (pure)	0	10.0
Aortic Stenosis & Insufficiency	0	1.3
Aortic Stenosis (pure)	2.6	1.1
Aortic Insufficiency (pure)	2.0	0.7
No of structural abnormalities	5.2	7.2
Total	100.0	100.0

Prognosis of Rheumatic Auricular Fibrillation—Taking all Rheumatic Heart cases (with and without fibrillation into account) there were 93 deaths in a series of 461 cases i.e. a death-rate of 20.2%.

Of the 88 cases of Rheumatic Heart Disease with Auricular Fibrillation, 6 died i.e. a mortality rate of 15.9%. The lower death-rate in cases of Auricular Fibrillation is probably accounted for by the fact that these cases are particularly amenable to treatment.

Syphilitic Auricular Fibrillation—There were only 2 cases in this group, both the cases being males (i.e. male to female ratio of 100% to 0%). One male was aged 34 years and the other 46 years, giving an average of 40 years for the group.

There were no deaths in this group.

The Hypertensive Coronary Group—The total number of cases of Auricular Fibrillation was 19 cases.

Sex Incidence—Of the 19 cases, 12 were males and 7 females i.e. 63.2% males to 36.8% females.

Age Incidence—The age-grouping of our cases was as follows—

Under the age of 20 years	No cases	0.0%
From 20 to 29 years	2 "	10.6%
" 30 to 39 "	6 "	31.6%
" 40 to 49 "	8 "	42.2%
" 50 to 59 "	2 "	10.6%
" 60 to 69 "	1 "	5.3%
Over the age of 70 years	0 "	0.0%

The highest incidence (42.2%) was observed in the fifth decade and in the fourth decade (31.6%) 73.8% of our cases were from 30 to 49 years of age, 10.6% were below 30 years of age and 15.9% were over the age of 50 years. The youngest was a female aged 27 and the oldest a male aged 68 years.

The average age for the group was 41.8 years.

Prognosis —Of the 19 cases, only 3 proved fatal i.e. death rate of 15.8%.

The Pulmonary Group (7 Cases) —In all the 7 cases of Auricular Fibrillation, in this group, there was associated Emphysema.

Sex Incidence —There were 5 males and 2 females i.e. 71.4% males and 28.6% females.

Age Incidence —The age grouping of our cases was as follows —

Under 30 years of age	No cases	0.0%
From 30 to 39 years	1 case	14.3%
„ 40 to 49 „	2 cases	28.6%
„ 50 to 59 „	2 „	28.6%
„ 60 to 69 „	2 „	28.6%
Over 70 years of age	No „	0.0%

The incidence was the same in the fifth, sixth and seventh decades of life. 85.7% of our cases were from 40 to 69 years of age, and 57.2% of cases were over 50 years of age. Only 14.3% of cases were below the age of 40 years.

The youngest subject was a male aged 36 years and the oldest, a female aged 68 years. The average age for the group was 52.1 years.

Prognosis —Of the 7 cases, 3 proved fatal i.e. a mortality rate of 42.9%.

The Miscellaneous Group —(35 cases) This group is inclusive of cases of Thyrotoxicosis, "old-age heart," extraneous toxæmias etc.

Sex Incidence —of the 35 cases, 27 were males and 8 females i.e. 77.1% males and 22.9% females.

Age Incidence —The age-grouping of the 35 cases was as follows —

Under the age of 20 years	No cases	0.0%
From 20 to 29 years	1 case	2.9%
„ 30 to 39 „	3 cases	8.6%
„ 40 to 49 „	11 „	31.4%
„ 50 to 59 „	12 „	34.3%
„ 60 to 69 „	5 „	14.3%
„ 70 to 79 „	2 „	5.7%
„ 80 to 89 „	No case	0.0%
„ 90 to 100 „	1 „	2.9%

The highest incidence was noted in the sixth (34%) and in the fifth (31.4%) decades of life. 65.4% (or two-thirds) of the cases were aged from 40 to 59 years. Only 11.4% of cases were below 40 years of age whilst 8.6% were over the age of 70 years.

The youngest subject was a male aged 26 years and the oldest, a male aged 100 years.

The average age for the group was 53.1 years.

Prognosis —Of the 35 cases in this group, 13 proved fatal i.e. a death-rate of 36.9%.

A Comparative Study of the various Aetiological groups of Auricular Fibrillation This has been incorporated in Table IV

The preponderance of males is noted in all the aetiological groups. An allowance must be made, however, for the unequal distribution of male and female beds at the K E M hospital, in the evaluation of results

The average age is strikingly different in the different aetiological groups. It is lowest in the Rheumatic group (33.6 years) and highest in the miscellaneous (53.1 years) and pulmonary (52.1 years) groups. Intermediate values are noted in the Syphilitic (40 years) and Hypertensive coronary (41.8 years) groups

The highest incidence of cases is noted in the fourth decade in the case of the Rheumatic group in the fifth decade in Hypertensive-coronary cases and in the sixth decade of life in the Pulmonary and miscellaneous groups. In other words, the average case of auricular fibrillation secondary to chronic lung disease or belonging to miscellaneous group, is about twenty years older than an average case of Rheumatic fibrillation

The prognosis of Auricular Fibrillation appears relative much better in the case of the Rheumatic and Hypertensive-coronary groups than in the case of the Pulmonary and Miscellaneous groups

TABLE IV

A comparative Analysis of the various Aetiological Forms of Auricular Fibrillation

Feature Investigated	* Rheu- matic	Syphi- litic	Bacte- rial	Hyper- tensive	Pulmon- ary	Miscel- laneous	All Forms
1 Number of cases	38	2	1	19	7	35	102
2 Percentage : males	63.2	100.0	100.0	68.2	71.4	77.1	73.5
3 Percentage females	36.8	0.0	0.0	31.8	28.6	22.9	26.5
4 Minimum age (years)	10	34		27	30	28	10
5 Maximum age (years)	56	40		68	68	100	100
6 Average age (years)	33.6	40	88	41.8	52.1	53.1	48.5
7 Decade (age) of highest incidence	4th	4 & 5	4	5th	6th	6th	5th
8 Death rate (%)	15.0	0.0	100.0	15.8	42.9	30.9	25.5

SUMMARY AND CONCLUSIONS

1 A statistical analysis is presented of 102 cases of Auricular Fibrillation, treated at K E M Hospital, Bombay, from 1941 to 1945 (inclusive)

The incidence of auricular fibrillation, in our series, worked out at 5.5% of all cardiac cases and 0.84% of all medical cases. Cases of paroxysmal fibrillation were not included in our study. The ratio of fibrillation to flutter cases, in our series, was 25.5 to 1.

2 The Aetiological relationships of our cases of Auricular fibrillation (102 cases) may be summarized as follows—Rheumatic group 37.3%, Syphilitic group 2%, Bacterial group 1%, Hypertensive group 18.8%, Coronary group 4.9%, Pulmonary group 6.9%, Miscellaneous group 34.8%.

3 The incidence of Auricular Fibrillation in individual Aetiological groups of Heart-disease cases was as follows—In the Rheumatic group, 8.2%, Syphilitic group 0.8%, Bacterial group, 5%, Hypertensive group 2.8%, Coronary group, 2%, Pulmonary group, 3.8%, Miscellaneous group, 11%.

4 73 5% of our cases of fibrillation were males and 26 5% females. The highest incidence of fibrillation was noted in the fifth decade of life (31 4%). 75 6% of cases were from 30 to 59 years of age, 6 9% were below the age of 20 years and 10 9% over the age of 60 years. The average age for the whole series was 43 5 years. The age-range being from 10 years to 100 years. The mortality rate for the whole group was 25 5%.

5 Rheumatic Group 63 2% of cases were males and 36 8% females. The highest incidence was noted in the fourth decade of life, the average age for the group was 38 6 years, the age-range being 10 to 56 years. The death-rate for the group was 15 9%.

Each aetiological group of Auricular Fibrillation has been analysed in the same manner.

(My thanks are due to the Dean and Honorary Staff of the KEM Hospital, for permission to publish this data.)

REFERENCES

- 1 BRAMWELL, C & KING, J "The Principles and Practice of Cardiology", London, 1942
 - 2 CADOT, R C J A M A (1914) 63 1481
 - 3 COORSON H Quart Jour Med (1929 80) 23 309
 - 4 COWAN, J & RITCHIE W T "Diseases of the Heart," 3rd Ed London 1935
 - 5 CUSHNY, A R : Jour Exp Med (1890) 4 327
 - 6 HERRMANN, G From Stroud's "The Diagnosis and treatment of Cardiovascular Diseases", I 1940
 - 7 JOLLY, W A & RITCHIE W T : Heart (1910 11) 2 : 177
 - 8 LEWIS, T Heart (1909 10) 1 300
 - 9 MACWILLIAM J A, Jour of Physiol (1887) 8 296 and (1888) 9: 345
 - 10 McELACHERN, D and BAKER, B M JR Amer Jour Med Sci (1932) 183 35
 - 11 ROTHBERGER, C J and WINTERBERG, H Wien Klin, Wchnschr (1909) 22 889
 - 12 STROUD, W D, LAPLACE L B & REISINGER, J A : Amer J Med Sci (1932) 83 48
 - 13 VAKIL, R J Ind Physician, (1942) 1 12
 - 14 VAKIL, R J Ind J Med Sci (1948) 1
 - 15 WEDD, A M and MULLINS, W L Clifton Med Bull (1932) 18 97
 - 16 WHITE, P "Heart Disease", New York, 1946
 - 17 WHITE, P D & JONES, T D : Amer Heart Jour (1928) 3 : 802
-

NEW METHODS FOR THE USE OF SULPHONAMIDES

by
DR S J GROSS, M D
BOMBAY

Since the advent of the sulphonamides and since the introduction of the antibiotics, most of the infectious diseases are treated with these substances. Though the antibiotics are generally more effective, the sulphonamides and its derivatives are still widely in use for a number of reasons, namely, easier administration, they are cheaper, more easily available, and they are not time limited. With the more extensive use of the sulphas it has been found that the results obtained tend to decrease in efficaciousness. The reduced efficaciousness of the sulphonamides and its derivatives has been ascribed to the appearance of sulpha-resistant bacterial strains. This applies especially to gonorrhoea where some years ago cure rates of 70-90% were claimed, while recently I saw a report with a cure rate of 25% only⁵. This deterioration in the efficaciousness of the sulphas does not apply to the pneumonias, as the pneumococci apparently do not develop any sulpha-resistance. Recently a number of reports have been published which suggest the possibility that certain bacteria may become penicillin resistant. Therefore it is desirable to find ways and means which would increase the efficaciousness of these therapeutical substances.

Sulphas and penicillin have one essential feature in common, i.e. both agents kill bacteria under conditions favourable to their growth, and do not kill them in the resting phase. For instance, it has been found that no bactericidal action was observed when penicillin was brought into contact with bacterial suspensions under conditions unfavourable to their growth (low temperature, exhausted culture medium). It has further been observed and confirmed that in a staphylococcal suspension over 99%, but not all of the bacteria are killed by penicillin. And the sulphonamides allow the bacteria to undergo several divisions in their presence before exerting their bactericidal action³.

The above findings indicate the eventuality that in some cases the parasites might not be eradicated completely. It is further possible that with this therapy the number of invading bacteria will be reduced to such an extent, that they will not exert a sufficient stimulus for the natural defence forces of the organism. This would allow a small number of bacteria to remain in the body, and later on to multiply there under suitable circumstances, especially as the administration of the drugs is usually discontinued after the abatement of the symptoms. This will allow an eventful relapse of the infection after some time. And this relapse might be complicated by the fact that in the meantime the bacteria might have become sulpha or penicillin resistant. It has also to be considered that the sulphas as well as the antibiotics do not stimulate the resistance and natural defence powers of the organism. Therefore one should also try to stimulate and to increase the natural defence powers of the organism in the fight against the infectious agents. This

activation of the immunizatory response in conjunction with the sulphas and antibiotics would allow a two-pronged attack against the infection

The organism responds to an infection with the production of anti-immunebodies. These immunebodies have been used in the fight against infection prior to the introduction of the chemotherapy, though the results obtained with the vaccine therapy have been moderate. It was found that the proteins contained in the vaccines induce a biological reaction in the organism which causes a kind of activation of the protoplasm and thus results in improvement and sometimes also in cure of an infection. This led to the introduction of the non-specific protein-shock therapy which aims at an increase of the natural defence forces of the organism.

Several theories have been forwarded about the mode of action of the protein therapy. Weichardt suggested that the parenteral administration of proteins and of protein split products stimulates and increases the activities and the functions of the organs. Others believe that the protein injections cause changes in the physical or colloidal state of the serum and thereby produce the therapeutical results. E. F. Mueller does not believe that the fever reaction is necessary for the therapeutic effect. He thinks that the injected proteins cause a kind of sterile infection in the organism and thus act as foreign bodies thereby inducing a stimulation of the defence mechanism of the body. Generally it can be said that protein and vaccine therapy cause an increase of the defence and of the resistance of the body. Milk injections have been used with good results for the protein therapy. It has been found that milk injections cause an increase of the leucocytes and that they stimulate the erythropoiesis in anaemic subjects. These injections are followed by an increased functional activity of the liver, as expressed by improved circulation in the liver and increased formation of bile and of lymph. These effects cause a detoxication and are important for the treatment of infectious diseases.⁶

It has been said that the sulphas are auxiliary to the antitoxins and that antibody formation is additive to the sulphonamide bacteriostasis. Therefore it is suggestive to assume that a combination of chemotherapy with proteins and/or vaccine therapy might be more efficacious than either method alone. In this connection the observations of Himmelweit⁴ seem worthwhile recording. This author found that a strain of staphylococci moderately resistant to both penicillin and bacteriophage became much more susceptible to destruction when exposed to the action of these two biological agents in combination. These observations have been confirmed by several authors. This combined action has been designated as a potentiating, conjoined or synergistic effect. The same synergistic effect may be obtained with a combination of sulphas with vaccines and milk, and this combination might be useful in cases which had become sulpharesistant, i.e., in chronic cases where the proteins will have a stimulating effect.

I have used the combination therapy in a number of affections. The results have been encouraging. It has to be mentioned that most of the cases were chronic ones, and most of them had previously been treated with penicillin and with sulphas. After trial and error the following method was evolved. One ampoule of Soluthiazole (M & B) was dis-

solved in either milk or milk-iodine to which vaccine in increasing dosage was added. These injections were given daily and deeply intramuscularly, preferably into the muscles glutei or vastus. The injections were sometimes somewhat painful, and in about 50% of the cases they were followed by a mild fever reaction. There were no other side effects. It has to be mentioned that sulphas were given orally at the same time. In the following I shall describe some of my experiences in the different affections.

The best results were obtained in the treatment of chronic gonorrhoea and of gonarthrititis. In these cases I gave injections of soluthiazole dissolved in milk, (milk-iodine was used in cases of gonarthrititis), to which gonovaccine in increasing dosage was added. In chronic cases there is usually a mixed infection, as there is a secondary infection with staphylo- and streptococci. In these cases a mixed gonovaccine was employed. The following cases may serve as illustrations.

(1) Mr K R, 28 years old Hindu, had a chronic gonorrhoea for one year. His main complaint was a discharge in the morning and beginning of a gonarthrititis in the right knee. He had been treated with several sulpha-products, and had also had some courses of penicillin. With these treatments there was regression of the disease, only to be followed by relapses. He was admitted to hospital where a further combined course of penicillin and sulphadiazine was given. At the end of this course there was still some discharge, but no gonococci were seen in the smear. Another smear taken after prostatic massage revealed a few isolated gonococci. He was then given a course of six injections of soluthiazole dissolved in 5 c c of milk-iodine to which a mixed gonovaccine was added. These injections were given daily together with sulphate tablets by mouth. The injections caused some fever. The discharge stopped after the 3rd injection, and the pains in the knee ceased. He was discharged after the 6th injection, and subsequent examinations of prostatic smears were negative. He has not had any relapse so far.

This method has been used with ambulatory patients too and the results have been uniformly good. I have tried the same methods in cases of gonarthrititis of more than 6 months duration. However, in those cases where the stiffness of the joint persisted for more than 6 months no improvement was obtained. For instance, (2) Mrs G S 22 years old, complained of pains and stiffness in the right hand for 8 months. A cervical smear showed Ge positive. She was started on Soluthiazole dissolved in milk-iodine and mixed with a mixed gonovaccine. She was given 15 of these injections, but there was no improvement, and the ankylosis persisted. The same method was quite useful in cases of chronic gonorrhoeic salpingitis and other chronic gonorrhoeic affections in females, as illustrated by the following case. (3) Mrs A V 28 years old, married, complained of discharge and pains in the lower abdomen for one year. A cervical smear showed Gonococci. She was put on sulphadiazine and given a course of 9 of the combined injections. She felt better, and the discharge became less after the 6th injection, and she was much better after the 9th injection. Repeated cervical smears were negative. It has to be mentioned that the patient had previously some treatment with penicillin and with sulphas.

I have used this method in a number of cases of gonorrhoea and its complications. Except in cases of long standing gonarthrits with marked ankylosis present, the results have been uniformly good. Encouraged by these results I have used a similar combination of sulphas with milk iodine and a vaccine in cases of rheumatism and of non-specific arthrits. There are controversial reports about the effect of the sulphas in rheumatoid and infective arthrits, some authors claim to have obtained good results, while others did not observe beneficial effect. Large scale trials with sulphonamides for the prevention of colds and of rheumatism in the American army seem to indicate that the sulphas may be of some value.¹ Therefore I have used a mixed staphylo-streptococcus vaccine combined with sulphas dissolved in milk-iodine for the treatment of arthrits and of painful joint-affectiions. I have used this method in more than 20 cases, and the results varied from very good to nil. Although the results were not always good, I believe that this method is quite a valuable addition to our therapeutic armamentarium. However, one word of caution is necessary. I found that these combined injections are not well tolerated by elderly patients, especially those over fifty and those who show signs of arteriosclerosis. In these patients the injections are sometimes followed by intensive headaches, and slight mental derangement lasting for one to two days.

Sulphonamides dissolved in milk to which the corresponding vaccine had been added were employed in a number of other infectious diseases, like typhoid, bacillary dysentery and *b. coli* infections. The results were encouraging, but the number of cases treated with this method was too small to allow a definite opinion. It is suggested that further investigations may be undertaken in these conditions.

Apart from its efficaciousness the combined sulpha-proteins shock therapy has the following advantages. It is well-established that the sulpha-drugs may cause a reduction of the leucocytes and in some cases even a leucopenia. Bliss and Long² have also reported that the sulphas are not effective *in vivo*, if the polymorphonuclear leucocytes have been depressed. These dangers are obviated by the combination of sulphonamides with milk and with vaccines. Milk injections cause an increase of the leucocytes, and prevent thus any eventual depressing action of the sulphas. Likewise the simultaneous protein shock will prevent any anaemia eventually induced by the sulphas.

Another effect of the combined therapy is that the milk and vaccine injections stimulate the natural defence forces of the organism. This will lead to a stronger attack on the bacteria by the organism and this will weaken the bacteria. The decrease in the resistance of the bacteria will enable the sulphas to exert a stronger and more potent action on the bacteria. Likewise it is possible that the defence forces of the body will have a stronger effect on parasites weakened by the action of the sulphas. The strengthening of the defence mechanism might also prevent an eventual multiplication of bacteriae after cessation of chemotherapy and would thus prevent the onset of relapses. It has also to be mentioned that the milk and vaccine injections induce fever in a number of cases, and White reported that the antibacterial potency of the sulpha drugs is increased manifold with higher temperatures.

SUMMARY AND CONCLUSIONS

A new method for the use of sulpha drugs and its clinical application is described. The method consists in the combination of sulpha-drugs dissolved in milk with corresponding vaccines. This combination is assumed to have a synergistic, conjoined or potentiating effect. The protein injections stimulate the natural defence forces of the organism, and promote thus a stronger action of the antibacterial drugs. This helps to prevent the onset of relapses and the appearance of drug resistant bacterial strains. Good results have been obtained in the treatment of chronic infections, especially of gonorrhoea, and in some cases of arthritis, rheumatism, lumbago and influenza. It is suggested to try this combination in a number of other infectious diseases.

REFERENCES

- 1 BARCLEY, P. E., KING LEWIS, F. L., *Lancet* (1945) 2: 751
 - 2 BLISS, E. A., LONG, *Jour. Am. Med. Ass.*, 1937, 109: 1524
 - 3 CHAIN, E., DUTHIE, E. S., *Lancet*, 1945 1: 652
 - 4 HIMMELWEIT, F., *Lancet*, 1945 2: 105
 - 5 SEEBERG, G. *ACTA DERMA to Venerologica* 1945 25: 301
 - 6 MUELLER, E. F., in Marle, W., *Lexikon der Therapie*, pp. 1061-72, Berlin, Urban & Schwarzenberg 1930
-

Critical Notes and Abstracts

SUPPRESSION AND TREATMENT OF MALARIA—C A BENTLEY *British Medical Journal*, Oct 9, 1948, p 691

In a letter to the Editor of the *British Medical Journal*, Prof Bentley, former Director of Public Health of Bengal, and Professor of Hygiene at the University of Cairo, tells of his experience with quinine during his long career in the Far and Near East

In the Jalpaiguri Duars of Northern Bengal, an area where spleen and parasite indices exceeded 90 per cent, he protected himself by systematic daily use of 1.5 grain tablet of quinine sulfate, if he developed any sort of symptoms (headache, sore throat, indigestion, etc.) quinine was not stopped, but the dose was doubled for a few days

In the Duars a large proportion of the European population took to systematic use of quinine. Since then, only three cases of blackwater fever occurred among Europeans who professed not to believe in quinine and only took it when they felt unwell

Many authors (including Bentley himself) consider blackwater fever to be consequent upon a sudden dose of antimalarial drugs after a long intermission. The onset of blackwater fever immediately after use of mepacrine, as reported by Wilson (*Medical Journal of Australia*, vol 2, 1943, p 414) suggests that this disease is not due to a hypersensitivity to quinine itself, but rather to a by-product liberated from the parasites themselves by an antimalarial drug

The moral appears to be that whatever the drug chosen for the suppression of malaria—whether it be quinine or mepacrine, and quite probably paludrine also—it would be wiser to take it daily rather than intermittently

THE TOXICITY OF LARGE DOSES OF PENTAQUINE (SN-13,276), A NEW ANTIMALARIAL DRUG—B CRAIGIE JR, L EICHELBERGER, R JONES JR, A S ALVING, TH N PULLMAN & C M WHORTON *Journal of Clinical Investigation*, vol 27, May 1948, p 17-24

Since a few years some substances of the group of 8-aminoquinolines are studied with care, because it has been shown that these substances (pamaquin, lately pentaquine and iso-pentaquine) when administered in combination with quinine, constitute at present the best method to treat patients with relapsing malaria, either caused by *P vivax* or *P malariae*

Craigie and co-workers treated 200 volunteers with pentaquine (SN-13, 276), with daily doses of 120 and 180 mg of the base. The purpose of their experiments was to define the margin of safety of the drug in clinical use. The routine dose of pentaquine being 30 mg daily only, one can understand that, if 120 or 180 mg are tolerated without serious consequences, 30 mg may be taken with safety

Most of the subjects experienced abdominal discomfort and methaemoglobinemia, but marked toxic symptoms were limited to those subjects receiving the drug without quinine. Further experiments are being taken, but at present one feels justified in saying that

- (a) toxic symptoms are severe when unnecessarily high doses (4 times the amount required for antimalarial chemotherapy) are taken,
- (b) toxic symptoms are lessened by the concomittant use of quinine

PENTAQUININE (SN-13, 276), a therapeutic agent effective in reducing the relapse rate in vivax malaria—A S ALVING, B CRAIG JR, R JONES, C M WHORTON, TH N PULLMAN & L EICHLBERGER *Journal of Clinical Investigation*, vol 27, May 1948, p 25—33

Pentaquinine was administered to 82 subjects in doses of 60 mg of base or less, daily. An additional group of 17 subjects without clinical malaria was included in toxicity studies.

Some of the subjects received quinine or paludrine concurrently with pentaquinine, all drugs being given every four hours for 14 days.

The concurrent administration of quinine sulfate (2 gm daily) with pentaquine (60 mg of the base) daily, was clearly more efficacious than pentaquine alone or the combination of pentaquine with paludrine.

RELATIVE RESISTANCE OF PL GALLINACEUM AGAINST QUININE THROUGH REGULAR ADMINISTRATION—

A TH KNOPPERS *Nederlandsch Tydschrift voor Geneeskunde*, vol 92, Sept 25, 1948, p 3034

The author, in a series of experiments, not corollated with those of Bishop and others, attempted to solve the question: Is it possible to heighten the resistance of avian malaria parasites against paludrine and Quinine? For this purpose, 7-day old chicks were first infected with 50 million parasites of *P. gallinaceum*. The infected animals were then treated with a sufficient dosage of these drugs to reduce the number of infected erythrocytes by one half, as compared with the untreated controls. This dosage was therefore not sufficient to eradicate the infection.

By this insufficient treatment a high-grade resistance against paludrine was reached in 3 months, the 30 to 40-fold of the initial minimum active dose become inactive. The strain of *P. Gallinaceum* which was thus made paludrine-resistant, remained normally sensitive to quinine, atabrine and the sulphonamides.

Analogue experiments with quinine proved that it is possible to increase resistance against this drug also, but only twofold. The quinine resistant strain of plasmodium remained normally sensitive to atabrine, paludrine, chloroquine, and the sulphonamides, but, strangely, became over-sensitive to substances of the group of 8 aminoquinolines: plasmoquine, pentaquine and isopentaquine.

One of the strains used in these experiments, which became somewhat quinine-resistant (laevo-rotatory), acquired the same property against cinchonidine (also laevo-rotatory). But against the dextro-rotatory homologues (quinidine and cinchonine) the increase of resistance was smaller.

When the administration of quinine was stopped during 26 weeks, resistance still remained about the same, after passage through the mosquito (*Aedes aegypti*) it was partially lost.

Knoppers is of opinion that in the practice of medicine the possibility of quinine resistance can be excluded.

STUDIES IN HUMAN MALARIA VII The protective and therapeutic action of quinine sulfate against St Elizabeth strain vivax malaria—G R COATNEY, W CLARK COOPER, D S RUEB, L S JOSEPHSON, M D YOUNG, & R W BURGESS
American Journal of Hygiene vol 47, Jan 1948, p 120

Thirty volunteers were each bitten by 10 *A. quadrimaculatus*, infected with the St Elizabeth strain of *Pl. vivax*, and were treated in different ways with varying doses of quinine sulfate U S P, containing 83 percent of quinine base (This quinine sulfate U S P is anhydrous and therefore contains about 1/10 more base than quinine sulfate of other pharmacopoeias)

Observation of the patients lasted for 18 months. All quinine doses were invariably administered every 6 hours, the daily dose being divided into 4 portions

A Protective tests (1) By administering 0.5 gm of quinine sulfate daily, during 25 days (4 days before, on the day of, and 20 days after exposure to infection) all 5 patients had their attacks of malaria delayed until 9 to 11 months after exposure

(2) By administering 0.25 gm of quinine sulfate daily for the same period of time, 4 out of 5 had early primary attacks, 2 to 3 weeks after exposure, in the fifth the delayed primary attack appeared on the 300th day

(3) Five controls (without quinine) had early primary attacks, parasitaemia becoming patent from 12 to 16 days after exposure

(4) Administration of quinine during 11 days (2 gm daily), 4 days before, on the day of, and 6 days after exposure, or 0.5 gm daily for the same period, had no success at all. All subjects treated as well as the controls, developed early primary attacks, parasitaemia becoming patent 12 to 15 days after exposure to infection

B Therapeutic trials (1) Twenty eight early primary attacks were treated with quinine sulfate for 6 days, 9 subjects got 2 gm, 10 got 1 gm, 9 got 0.5 gm daily. Results may be summarised as follows: "Parasitaemia cleared and fever was controlled in all 28 subjects, the rapidity of action being roughly proportional to the dosage used." These are the words of the authors

However, when studying their table (3), one finds clearly that 0.5 gm of quinine sulfate daily was definitely insufficient for some subjects. 4 out of 9 patients had recrudescences within 3, 6, 11 and 15 days, the others relapsed after 8 to 9 months

All patients treated with 1 or 2 gm of quinine sulfate daily relapsed after several months only, and in this respect one cannot speak of the action of the drug being proportional to the dosage used. In these experiments there certainly existed a certain proportion between dosage and immediate results, when comparing these after 1 and 2 gm daily, one finds clearance of the blood in 4 and 3 days, resp., afebrile temperature in 2 days and 1 day. This difference however, is certainly not important, it is more important that the patients who were treated with 6 gm of quinine sulfate in 6 days must have had a much better time than their co-patients who got 12 gm in the same period of time, and who must have suffered from cinchonism

(2) In 5 persons 16 late attacks (including relapses) of St Elizabeth strain vivax malaria were treated with 2 gm of quinine sulfate daily

for 6 days. As in this series no comparisons were made between different regimens (e.g., 1 or 2 gm daily), we can only remark that, as in the first series, where 0.5, 1 and 2 gm daily were tried, no difference was seen between the latter two as regards relapses, it seems justified to suppose that 1 gm daily would have given the same results as 2 gm daily.

Plasma concentration of quinine—The authors determined plasma quinine daily, 3 hours after the morning dose of the drug. Recently the determination of plasma quinine has come into the fore, mainly through publications of *Brodie & Udenfriend* and *Shannon*. It becomes clear that the amount of quinine in blood plasma (mg per litre) is not correlated with therapeutic results, if one studies the tables 3 and 4

Patient A 20	with 3.0 mg	quinine	per 1	relapsed after	11 days
" A 24	" 2.0 mg	"	"	"	202
" A 15	" 4.8 mg	"	"	"	15
" A 23	" 3.0 mg	"	"	"	275
" A 25	" 4.3 mg	"	"	"	208
" A 30	" 2.9 mg	"	"	"	276
On the other hand					
Patient A 11	with 15.6 mg	quinine	per 1	relapsed after	251 days
" A 17	" 4.4 mg	"	"	"	252
" A 10	" 8.3 mg	"	"	"	301

In 9 patients who took 0.5 gm of quinine daily, the mean plasma concentration varied between 1.9 (A 9) and 5 (A 45), in 10 patients who took 1 gm daily between 4.3 (A 25) and 10.3 (A 8), in 12 patients who took 2 gm daily between 4.0 (A 44) and 15.6 (A 11).

So, patient A 44 took 4 times the dose of patient A 45 and still had a lower plasma concentration.

All these patients relapsed after 251, 256, 268, 271 and 276 days, respectively. Only A 9 recrudesced promptly after 6 days.

Another example. Patient A 24 took 1 gm daily; his plasma contained only 2.7 mg of quinine per litre and it took 3 days before his smear was negative. Patient A 11 took 2 gm daily; his plasma contained 15.6 mg per litre, nearly the sixfold of A 24.

These examples clearly show that determination of the plasma concentration of quinine has little practical value, if any, in judging the therapeutic effects of quinine doses.

CURE OF CHRONIC VIVAX MALARIA WITH PENTAQUINE

—L. T. COGGESHALL & F. A. RICE. *Journal of the American Medical Association*, vol. 139, February, 12, 1949, p. 437-439.

So far treatment of malaria has been characterized by the failure to obtain permanent cure, especially in vivax and quartan malaria. Quinine and the newer synthetic antimalarials afford prompt relief in the acute attack, but relapses occur in a high percentage of patients.

Since 1930 we know that these relapses may be reduced in number by treatment with quinine, combined with substances of the 8-amino quinoline group. First among these was plasmochin (now called pamaquin), then came pentaquine, synthesized by DRAKE.

Many very favourable reports, both about quinine-pamaquin and quinine-pentaquine have been published, but nearly always the reports mentioned annoying symptoms in a rather large percentage of cases: cinchonism and epigastric troubles with methaemoglobinemia.

These symptoms were certainly caused by the rather high dosage of both drugs. Most authors used 2 grammes of quinine, with 60 mgm of pentaquine daily. *Coggeshall* and *Rice* started with a 14-day regi-

men of 2 gm of quinine daily also, combined, however, with 30 mgm of pentaquine base. They wrote "Since the amount of quinine was chosen arbitrarily and because many of the first patients treated complained of symptoms of cinchonism, the amount given was reduced to 1 gm per day." Thus, 67 patients got this moderate daily dose, which proved to be as effective as the larger one. To quote the authors "The dosage of quinine when decreased from 2.0 to 1.0 gm seemed to be just as effective."

Of 185 patients, the majority of which was experiencing relapses every 4 to 6 weeks prior to treatment, 163 had no further objective findings referable to malaria, 10 were verified failures, with blood smears yielding parasites, the remainder had chills but no parasites could be detected in their blood smear. It is not sure whether or not the latter group ought to be considered as failures.

Anyhow, results have shown that quinine pentaquine, in moderate doses like prescribed by *Coggeshall* and *Rice*, very nearly succeeded in radically curing vivax malaria.

THE PROBLEM OF TRICHINOSIS

Within recent years in the United States a number of surveys of the incidence of trichinosis in autopsies have been made and these show an average of 16 per cent infection. This means that at least 16 per cent of persons in the United States, at the time of death, have trichinosis. In Gould's series of over 1,200 autopsies, a total incidence of trichinous infection of 22 per cent was found. In succeeding decades the incidence became progressively greater, so that in the 80's an incidence of 33 per cent was found, therefore, the older the person the more chances he has had of exposure to this infection.

At autopsy larvae may be sought by the usual microscopic method of sectioning and by the compression and digestion methods. When a single block of diaphragmatic muscle was sectioned 2 per cent of the infections were found. By compression of a 1.0 gm portion of diaphragm 11 per cent were detected, but when 10 portions of 1.0 gm each were examined 29 per cent of the infections were found. When both methods were used the author was able to recover trichinae from over 30 per cent of bodies examined.

In large part, therefore, the incidence of infection as determined at autopsy will depend upon the method used. In the digestion method, artificial gastric juice (1 per cent pepsin and 1 per cent hydrochloric acid) is added to the ground muscle in a container. The mixture is stored in an incubator-room overnight to digest the muscle and cyst walls. The larvae, however, resist digestion. When the mixture is then filtered the organisms are recovered.

Methods that may be used for diagnosis of the disease include examination of the blood for eosinophilia, immunologic tests (intradermal test, blood precipitin test, and complement-fixation test), demonstration of larvae in the host, in the blood, in the cerebrospinal fluid, in skeletal muscles and demonstration of larvae in the suspected meat. The leukocyte count is generally increased in the disease, with eosinophilia as the most important sign. The degree of eosinophilia is not an index to the severity of the disease.

The common symptoms of the disease are (1) Constipation or diarrhea, either of which may be severe and protracted. (2) Fever

(3) Ocular (4) Muscular pain (5) Respiratory symptoms (6) Neurologic symptoms (7) The cardiovascular symptoms

Since 1.5 per cent of all hogs in the United States are trichinuous, this means three servings out of 200 servings per person per year would be trichinuous pork, and that during the lifetime 200 servings of trichinuous pork will be offered. Fortunately, most of the meat will contain dead trichinae if it is properly prepared. However, only one meal with one living trichinae is required to produce the infection. It is recommended that the Government require that all pork intended for sale shall be so processed as to render it free from viable trichinae.

(Coudé, Sylvester F. Detroit, Mich. Diagnosis and Treatment of Trichinosis. Postgraduate Medicine 5: 247 April 1949)

ANEMIAS IN PREGNANCY

In a recent article by Wolff and Limarzi, the clinical management of the anemias of pregnancy is discussed. It was stated that excessive loss of blood during pregnancy is the greatest cause of death from childbirth, and that in order to lower this mortality all factors that are contributory must be eliminated. A healthy woman may lose 500 to 600 c.c. of blood during delivery without ill effect, while such blood loss may be disastrous in a severely anaemic individual. Correct diagnosis of the anaemia as to type and cause is essential. Therapy must be rational and proper. Then the patient will enter labour ready to combat possible blood loss.

There is a definite increase in blood volume during pregnancy. This is maintained until after delivery except for a slight reduction as the patient approaches term. This increase in volume is due entirely to an increase in the plasma content of the blood. The blood cells are produced at a normal rate, similar to that in non-pregnant individuals. Treatment is not needed in such cases and so called routine prophylactic anti-anemia therapy is contraindicated.

The careful management of the anemias of pregnancy primarily demand an accurate diagnosis of the anemic state. Blood replacement is a valuable method of rapidly bringing the blood values up to safe levels. The use of blood transfusion as a therapeutic agent in the anemias of pregnancy has been strongly recommended by the authors. Strict adherence to details and the complete co-operation of the laboratory technicians, the nurse and the doctor is stressed. The laboratory technician must see that the blood is correctly typed, cross-matched, and the Rh factor determined.

The doctor must check on these factors as he is the one legally responsible for errors. He must also be certain that the transfusion equipment is sterile and pyrogen free. The blood must be warmed to room temperature and must be given slowly.

Forty drops per minute is the proper speed for at least the first hundred c.c. The obstetrician can competently diagnose and treat most cases himself with the use of simple routine laboratory procedures. Yet whenever the anemia is severe or does not respond to simple therapy, co-operation with the hematologist is essential.

(Wolff, John R. Chicago, Ill. M.D. and Limarzi, Louis R. M.D. The Clinical Management of the Anemias of Pregnancy, American Practitioner Vol. III: 473 April 1949.)

PERSONALITY IN HYPERTENSION

The authors have made a comprehensive study of the degree of association between various possibly relevant personality patterns

in hypertensive and non-hypertensive persons. The study was divided into three groups (a) Group I which was subdivided into two groups Neurogenic hypertension, and other types of hypertension, (b) Group II—personality disorder without hypertension, and (c) Group III—chronic somatic disorder.

For the personality ratings, experimentation with a number of habitual patterns of reaction to crisis and of interpersonal relations was made of which only the following seemed feasible: hysteria, anxiety, depression, obsessive-compulsive behavior, subnormal assertiveness and impulsiveness.

The patterns rated have little to do with either the age at detection of hypertension or the duration of hypertension and with few exceptions, the patterns defined were present at the rated levels long before the detection of hypertension. Statistically significant degrees of association are found for "obsessive-compulsive behavior" ($r=0.44$ plus or minus 0.10) and for "subnormal assertiveness" ($r=0.38$ plus or minus 0.10).

The described positive associations between presence of hypertension and certain personality ratings do not signify an etiologic relation between the significant patterns and hypertension, but only that there is concomitant variation of the two variables. The absence of significant differences in the ratings for neurogenic and for other types of hypertension—endocrine, renal, mixed—is noted. By much more laborious study of far fewer subjects, this method should prove useful in similar investigations.

(Cressel Gregory C. St. Louis, Mo. et al. Personality Factors in Arterial Hypertension. Journal of the American Medical Association 140: 265-272 May, 1949.)

HEMORRHAGE ARISING FROM ABNORMAL HEMOSTASIS

Summarized data on a series of patients with spontaneous bleeding who had a similar clotting abnormality was recently presented by Allen, Grossman, Elghamner, Moulder, McKeen, Jacobson, Pierce, Smith, and Crosbie of Chicago. This clotting defect was characterized by an increase in the protamine titration and was frequently associated with a prolongation in the whole blood clotting time. The blood of the patients comprising this study showed an increased protamine titration when the prothrombin level was normal or near normal, when fibrinogen levels were not abnormal and when fibrinolysin was not grossly disturbed.

Many of these patients also had severe thrombopenia. In others, hemorrhage occurred when the platelet count was normal. The bleeding in most of these patients responded to adequate therapy with toluidine blue and/or protamine sulfate. It is pointed out that both of these agents are capable of reacting with several endogenous compounds in the body other than heparin. Some of these endogenous compounds are heparin-like, but the rest appear unrelated to heparin. The defect presented by thrombopenia, did not respond to this form of therapy. In those few patients with idiopathic thrombopenia and an increased protamine titration who did respond to the dye, the response was inadequate to warrant withholding splenectomy. Thrombopenia was observed to occur with or without an increased protamine titration and *vice versa*.

While these two changes were frequently associated, they appeared to be independent phenomena. Many of the patients state they felt better after toluidine blue was administered. While this response may have been due to the psychologic effect of the events commonly associated with therapeutic measures of this type, it is also known that the dye is capable of increasing the oxygen uptake of the tissues.

Patients whose bleeding was associated with malignant disease were frequently temporarily relieved of the distress of bleeding, although bleeding tended to recur in this group unless toluidine blue was administered at regular intervals.

(Allen J. Garrett, University of Chicago, Chicago, Ill.; Grossman, Burton J., Elghammer, Richard M., Moulder, Peter V., McKen, Charles L., Jacobson, Leon O., Pierce, Milla and Smith, Taylor R. and Crosbie, James M.: Abnormal Bleeding. *Journal of the American Medical Association* 139: 1251 April 1949.)

SCHICK TEST RESULTS AFTER DIPHTHERIA TOXOID INJECTION

The results of the Schick test performed, with controls, on 121 children 36 to 38 months after they received a single injection of protamine diphtheria toxoid are reported by Ross. All of them had positive reactions to the Schick test before they received the toxoid, and they had not been tested in the interval. The ages of 98 of the children at the time of the second test ranged from 42 months to five years, the rest were between 68 months and 12 years old.

In nine children the results was read four days after the injection of the Schick toxin and again three days later. No change in the four day reading occurred, with the exception of one result which was doubtful on the fourth day and positive on the seventh. Thirty-two were seen seven days after the injection. Of the 121 children, the reaction of six to the Schick test were positive and the reaction of one was pseudo-positive. Therefore, approximately 95 per cent were, presumably, still immune.

The ages of the children with positive reactions at the time of the test were 42, 44, 46, 53, 95 and 125 months. It is of interest that all six positive reactors were among those subjects the total number of whom was 58, tested in the months of October, November and February, while among the 63 tested in the months of April and June there were none with positive reactions. The artificially immunized children lived in their parents' homes, contact with actual cases of diphtheria was probably nil, while contact with carriers cannot be estimated.

In spite of the satisfactory immune status of these subjects, it is recommended that two doses of protamine toxoid be administered rather than one. The belief is based on the considerably larger percentage of children who produce greater amounts of antitoxin (1/10 unit or more) after two injections. Thus, protection will be more prolonged in a greater proportion of children.

(Ross, Victor, Ph.D., New York, N.Y.: Results of Schick Testing Three Years After the Injection of Protamine Diphtheria Toxoid, *American Journal of Diseases of Children* 77: 450 April 1949.)

RADIOIODINE IN THE BLOOD

McConahey, Keating, Power have undertaken the present study to (1) examine directly the behavior of radioiodine in blood after its oral administration to persons who have varying states of thyroid function, (2) compare the disappearance rate of radioiodine in blood as determined directly from observations in the blood itself with esti-

mates of this same value obtained from urinary studies, and (3) examine the appearance in the blood of organically bound radioiodine

Levels of total radioiodine in the blood after oral ingestion of I^{131} in the form of iodine show significant differences in various thyroid states. Mean concentration of radioiodine in the serum was 2.06 per cent of the dose per liter in cases of myxedema, 1.28 per cent in euthyroid persons and 0.49 per cent in cases of hyperthyroidism was noted eight hours after ingestion.

The curve of total radioiodine in serum plotted against time has three components: (a) an initial rapid increase followed by a brief, rapid fall, regarded as reflecting gastro-intestinal absorption, and equilibration with body fluids; (b) an exponential fall, regarded as reflecting disappearance of radioiodine as iodide from the blood into the thyroid, the urine and other sites of disposal, and (c) a third phase which indicates the appearance in the blood of organically bound radioiodine.

The authors estimated the disappearance rate of radioiodine from the blood from the curve of excretion in the urine, and found the rate reflected variations in thyroidal function, being more rapid than normal in hyperthyroid subjects and less rapid than normal in hypothyroid ones. No significant difference was disclosed when the rate of disappearance of radioiodine from blood estimated directly from blood itself with estimations of the same rate determined from simultaneous observations of urinary excretion of radioiodine was compared.

This latter method therefore appeared to be an appropriate means of estimating the disappearance rate of radioiodine from the blood. Precipitable radioiodine appeared in the blood much sooner, rose more rapidly and reached higher concentrations in hyperthyroid than in euthyroid persons. A small concentration of precipitable radioiodine was observed in a patient who had myxedema. Even though the method employed is relatively insensitive and inaccurate it appeared likely, however, that with more sensitive and accurate methods of analysis the rate of increase of organically bound radioiodine in blood and the maximal concentration achieved can be compared with the concentration of protein-bound iodine measured by chemical methods in order to obtain a measure of turnover rate of protein-bound iodine.

(McConahey, William M., Mayo Clinic, Rochester, Minn. et al. *The Behavior of Radioiodine in the Blood*. Clinical Investigation 28: 101-108 March 1949.)

The Indian Physician

VOL VIII NO 12

DECEMBER 1949

WHOLE NO 96

Original Contributions

SOME OBSERVATIONS ON THE 1949 EPIDEMIC OF POLIOMYELITIS IN BOMBAY

by

D D VORA, MD F.C.P.S. M.R.C.P. (Lond.)
Physician, Municipal Group of Hospitals Sion
BOMBAY

An opportunity occurred to observe some aspects of Poliomyelitis, when the Municipal authorities decided to admit the cases occurring in the city in Municipal Group of Hospitals Sion. But it must be said that cases were received from near vicinity of Bombay like Thana and an occasional case from farther than that. The first case was received on July 28, 1949. The last case included in this series was admitted on October 14, 1949. Since then, three cases have been admitted, which are not included in the present series.

In all 110 cases were admitted to the polio-wards, with the presumptive diagnosis of Acute Anterior Poliomyelitis. Of these 82 were clinically diagnosed Acute Anterior Poliomyelitis, and the rest comprised various conditions which will be mentioned under the heading of differential diagnosis.

It was not possible to test each individual muscle in all our cases, as most of the patients were of the age-groups from six months to two years, in whom the active co operation was not possible.

Due to lack of facilities for electrical testing, it was a further handicap to the accurate localisation of the affected muscles, and also as there was no adequate laboratory facilities, it was not possible to get reliable results of the examination of cerebro-spinal fluids of all the cases. Hence no mention will be made of the same in the following remarks.

Treatment—In order to obtain uniform information the house officers and the nursing staff were given printed instructions. The treatment given to the patients mainly aimed at strict isolation of the case and the attendants. This was achieved by reserving the services of few of menial and nursing staff exclusively to polio-ward. The nursing staff, the menials, and the medical officers visiting the ward were provided with masks and gowns for their safety and for preventing them as carriers. The relatives were not allowed to visit the patients in the ward. Tonsillectomies are suspended since the beginning of the admission of the polio cases, in order to avoid bulbar complication. No case of cross-infection has occurred in the hospital, nor has any been reported from the staff or their immediate contacts.

All patients were given either a salicylate or a bromide mixture on admission. Emil Smith (1948) has reported good results of Priscol therapy. Bubbet al (1948) have reported favourably on the D H E 45 or Di-hydroergotamine. In view of this, it was decided to use them in conjunction with control cases who were not given these drugs. In the beginning every alternate case was treated as control and with D H E 45. Later on, Priscol was added to the trial, putting every third case on Priscol. After the acute stage was over, care was taken to prevent contractures by massage and passive movements. At the end of six weeks of disease the cases were discharged and directed to the Rehabilitation Centre for further Orthopaedic treatment, if required.

Priscol is a synthetic vasodilator and is supposed to act beneficially by increasing the blood-supply to the affected limb, which is cold and partially ischemic due to the vasospasm. D H E 45 has sympatholytic action and the beneficial effects are thought to be due to relief of the limb from the vaso-spasm. The dose of Priscol was 5 mg—4 hourly for a fortnight, to the children. D H E 45 was given to adults in dose of 2 mg—8 hourly for a week intramuscularly followed by 8 drops—8 hourly orally for a week. In children it was given 8 drops—8 hourly orally for a week (15 drops=2mg).

Sex-Incidence —

Males	Females	Total
48	34	82

In this series, there were 48 males, as against 34 females. The males are said to suffer somewhat more frequently than females. In this group of females, one patient aged 23 years was pregnant, four months. Pregnancy was not affected till 45th day of the disease.

Age-Incidence —

Age	Males	Females	Total
Up to 6 months	3	2	5 (6%)
7—12 months	10	13	20 (35.5%)
13—24 months	10	9	25 (30.5%)
25—36 months	6	4	10 (12%)
37—48 months	1	3	4 (5%)
49—60 months	0	0	0
6—10 years	3	1	4 (5%)
11—15 years	0	0	0
16—25 years	0	2	2 (2.5%)
25 years and above	3	0	3 (3.5%)
Total	48	34	82

It is believed that children under the age of one year are rarely attacked and children below the age of six months are seldom affected due to transplacental immunity from the mother. Most sufferers are between the ages of two and four years. After the age five years the susceptibility diminishes and the disease is rare after the age of 25 years. In the present cases, youngest patient was 1½ month old and the oldest was 80 years of age. Most of the cases, 35.5%, of the total fall under the age-group 7-12 months.

Kelleher (1947), observing on some aspects of the 1947 epidemic of U K, quotes the age incidence, in his 66 cases as follows —

Age	Percentage
Under 5 years	33
5—15 years	40
Over 15 years	37

The youngest patient of his was eight months old and the oldest one was 41 years

Abortive Cases —Those cases were diagnosed as abortive which showed slight transient weakness and normal jerks There were 10 such cases, which are detailed below —

Age	Males	Females	Total
18—24 months	4	1	5
25—36 months	0	2	2
6—10 years	3	0	3

Distribution of Paralysis —(As presenting symptom) Generally the lower limbs are affected more than the upper limbs The bulbar form is not frequent The distribution is as follows in the present group —

Spinal distribution 75 cases (91.5%)

(a) Upper extremities—7 cases (8.5%)

(b) Lower extremities—56 cases (68%)

(c) A combination of upper & lower extremities—8 cases (10%)

(d) Quadraplegia—4 cases (5%)

Bulbar—involved the facial nerve nucleus, 6 cases (7.5%)

Encephalitic—1 case (1%)

In the upper extremities group, only one extremity was involved in all cases In these cases, one died, five were left with residual paralysis and one had no residual paralysis

In the group of the combination of the lower and upper extremities, one upper and two lower extremities were affected in 2 cases In 6 cases, one upper and one lower extremities were affected, the distribution being ipsilateral in 5 cases and contralateral in 1 case In this group, one died of diaphragmatic paralysis and in 1 cause of death could not be determined ante-mortem Residual paralysis was seen in 5 cases and one was discharged without any neurological abnormality

From the cases, with the involvement of the lower extremities alone, 10 were abortive, 5 were not left with any paralysis, 37 had residual paralysis and 4 died The cause of death was diaphragmatic paralysis in 1, vasomotor paralysis in 2, and terminal rise of fever in 1 One extremity was involved in 29 cases, the rest with the involvement of both extremities Among these were also the cases with involvement of paravertebral muscles in 2, cervical muscles in 1, unilateral abdominal muscles in 1, cervical with paravertebral in 1, ipsilateral dome of diaphragm in 1, and ipsilateral facial involvement in 1 case

From amongst the cases with quadraplegia, two had unilateral affection of the diaphragm All the four cases of quadraplegia died of respiratory paralysis

All the cases of the bulbar type showed the affection of the VII cranial nerve distribution One case also had the weakness of the cervical muscles No death occurred in this group One left without any abnormal neurological sign but five had residual paralysis

The one case with the encephalitic involvement, showed the Parkinsonian tremors on one side There was no past history of ophthal-

moplegia nor somnolence Patient had fever for few days preceding the tremor.

Laha (1945) quotes distribution of paralysis in 1166 cases of Lovette, from the New York epidemic of 1916

Group	No of Cases	Percentage
Both legs	338	29%
One leg	302	25%
Both legs + both arms	127	11%
Both legs + one arm	101	8.5%
One arm	83	7%
Homolateral arm + leg	88	8.5%
One arm + opposite leg	29	2.5%
Both arms	3	3%
Both arms + one leg	20	2%
Girdle cases	57	5%
Facial alone	38	3.5%

Differential Diagnosis —Acute anterior poliomyelitis is generally to be distinguished from acute transverse myelitis, acute infective polyneuritis and tuberculous meningitis In this series, a variety of cases were referred to us with a label of poliomyelitis This could be attributed to recent consciousness about poliomyelitis in the city There were 28 such cases They included the following conditions —

Hysterical aphonia, hiccough, dysphagia and paresis, tetany, syphilitic spinal paralysis, convulsions in children due to worms, post-traumatic inability to use the extremity, ataxia, guinea-worm abscess, acute attack of bronchial asthma, tuberculous enteritis of long standing

Of the above, three cases which were very instructive are briefly mentioned here

A young man aged 30 years was admitted to the polio ward with history of fever for a day, intense pain in the thighs and inability to move the lower extremities Examination revealed weakness of the flexors of both thighs, normal knee and ankle jerks, marked tenderness of thighs, symmetrical bilateral firm swellings of thighs on their antero-lateral aspects, giving the appearance of inverted champagne-bottles This was at first thought to be due to spasm of the quadriceps femoris When after four days of observation, neither the pain nor the fever subsided, an X-ray plates of the thighs and the hips were taken These showed the presence of calcified guinea-worms in both the thighs and in the abdominal wall Penicillin and sulphadiazine relieved the patient The swellings of the thighs softened and had to be incised and evacuated

A girl of 14 years of age, with slightly stunted growth for her age, was admitted with history of fever previously, vomiting and intense pain in the limbs On examination, neither weakness nor change in the reflexes was noted But a very mild carpo-pedal spasm was observed Blood-serum calcium was 4 mg/100 ml The patient died after a few days of anuria and uraemia

A boy about 9 years of age, in an acute attack of bronchial asthma, was thought to be suffering from diaphragmatic paralysis, which was discovered on fluoroscopy done without the preceding clinical examination The patient had low fever The diaphragm was immobile Patient had prolonged expiration with dry sounds Adrenaline $\frac{1}{2}$ ml subcutaneously gave prompt relief

Results —The results vary from epidemic to epidemic. The death-rate varied from 1%—48%. Emil Smith (1949) quotes of the cases from 1937—1947, at Brooklyn as follows —

<i>Total Cases</i>	<i>Residual paralysis</i>	<i>Deaths</i>	<i>Recovered</i>
1172	607 (51%)	51 (4.25%)	565 (48.25%)

In the discussion in Primer on Polomyelitis, mention is made of the mortality-rates of various epidemics

New York, 1916	25.2%
Sydney (Australia), 1937, less than 1%	
Manitoba, 1941—%	

Results of the cases —

<i>Result</i>	<i>Deaths</i>	<i>Recovered</i>	<i>Residual paralysis</i>
D.H.E. 45	3	4	25
Priscol	1	2	4
Control cases	7	2	24
Total	11 (15.5%)	8 (11%)	53 (73.5%)

Results of D.H.E. 45 —

	<i>Males</i>	<i>Females</i>	<i>Total</i>
Deaths	2 (12%)	1 (7%)	3 (9.5%)
Recovered	1 (6%)	3 (20%)	4 (12.5%)
Residual paralysis	14 (82%)	11 (73%)	25 (78%)
Total	17 (100%)	15 (100%)	32 (100%)

Results of Priscol —

	<i>Males</i>	<i>Females</i>	<i>Total</i>
Deaths	1 (14%)		1
Recovered	2 (29%)		2
Residual paralysis	4 (57%)		4
Total	7 (100%)		7

Results of the cases treated as control —

	<i>Males</i>	<i>Females</i>	<i>Total</i>
Deaths	5 (30%)	2 (12.5%)	7 (21%)
Recovered		2 (12.5%)	2 (6%)
Residual paralysis	12 (70%)	12 (75%)	24 (73%)
Total	17 (100%)	16 (100%)	33 (100%)

Results according to the sex —

	<i>Males</i>	<i>Females</i>
Deaths	8 (10.5%)	3 (10%)
Recovery	3 (7.5%)	5 (16%)
Residual paralysis	30 (73%)	23 (74%)
Total	41 (100%)	31 (100%)

In this series, the females have shown a better reaction to recovery, less death rate, and less number of cases of residual paralysis. The results of the Priscol therapy could not be considered according to the sex, as coincidentally all the patients who were given Priscol were males.

All those who presented with quadruplegia, died of respiratory paralysis. As the virulence of the virus varies from epidemic to epidemic, beneficial results cannot be definitely attributed to any particular drug, unless and until the same drugs are tried with control cases in every epidemic and the results summated.

SUMMARY

- 1 The present series shows a higher incidence of polio in the males
- 2 The maximum number of cases belonged to the age-group, 7—12 months
- 3 The females have shown on the whole a favourable reaction to the polio
- 4 The list of differential diagnosis, as encountered, is appended
- 5 The results of D.H.E. 45 and Priscol are presented with the controls, though the number of cases is small

I am indebted to Dr N D Patel Hon Physician K E M Hospital, Parel, Bombay for his guidance and advice, and Dr S V Joglekar Superintendent M G Hospitals Sion for his permission to publish the cases. My thanks are also due to Sandoz Products Ltd, for the supply of D.H.E. 45 and to Ciba Pharma Ltd for the supply of Priscol.

REFERENCES

- BUBB W (1948) *Schweiz Med Wschr* 78 1262
 EMIL SMITH et al (1948) *New York State Journal of Medicine* 48 2608—2611, Dec 1948
 EMIL SMITH et al (1949) *Journal of Paediatrics* 34 1 11 January 1949
 ——— (1949) *J A M A* 131, 1411—1499, August 1949
 KELLEHER W H (1947) *B M J* 2 291 295, August 1947
 LAHA P N (1948) *Indian Med Gaz* 80 537 538, Nov 1948
 NELSON W E (1947) "Test Book of Pediatrics" 479-485, 1947
 RUSSELL BRAIN W (1945) 'Diseases of the Nervous System,' 448-454, 1945
-

PITFALLS IN CARDIAC DIAGNOSIS

by

V V SHAH, M D , M R C P (Lond) M R C P E

In the course of medical practice, one comes across certain findings which may be mistaken as heart disease. It is well known to us that if a patient otherwise healthy, is told that his present symptoms are due to heart disease or myocardial damage, he views this with anxiety and seriousness, leading an invalid life. A patient when he was told that he had myocardial damage, narrated the anxiety and sleepless nights through which he passed, only to learn later that his heart was normal. Hesitating opinion on the part of physician or in trying to steer safe and remain equivocal, paves a way to cardiac neurosis and a life of cardiac invalidism. The prognosis, management and treatment also depend upon the proper evaluation of these symptoms and signs. I shall therefore discuss with you certain observations which are likely to be interpreted as heart disease, but which can be partly or wholly explained by extra cardiac causes or as mere physiological variations.

The first symptom that I propose to discuss is praecordial pain. As a cardiac symptom, this is the commonest met with in consulting practice. It is referred to decide, "Is it a cardiac pain i.e. pain of cardiac ischaemia or myocardial infarct? If not so, what is the cause?" In an analysis of one hundred and fifty consecutive cases referred in private practice, for heart disease or suspected of heart disease, 50% were referred for praecordial pain, out of which two-thirds belonged to a group of extracardiac pain and one-third only to cardiac pain. Even in such a small series as this, you will see that extracardiac pain is very frequent. I am not surprised at this because there are as many causes of pain as there are anatomical structures round about the heart. The common causes which I have come across are—affections of mammary gland like—mastodynia, chronic mastitis, tight corsets and ill-fitting supports, muscle cramp and muscle strain, myofibrositis, arthritis of sterno costal and cost chondral articulations, flatulent dyspepsia-gastric or colonic distension, oesophageal and cardiospasm, peptic ulcer etc. Complete details about the praecordial pain should be obtained viz exact site or location, its character, what brings it on? What relieves it? Does it come on even at rest? Mode of onset and duration and any associated symptoms. Common sense evaluation after a careful and searching clinical examination with an unbiassed mind will prevent an error and the labour will be rewarded by a positive clinical diagnosis.

Even after careful exclusion of these causes in extracardiac pain, the commonest cause is neurotic or psychosomatic pain. Paul White also found this kind of "heart-pain" to be the commonest. It is common in young adults, females more than males. It is usually located in infra-mammary region. It is a dull or heavy ache but may be interspersed with momentary jabs, stabs or pricks. Its production is not dependent on physical effort and it also lasts while at rest. Its duration is long, and it may radiate to left arm. It is aggravated by worry, pressure of work, or emotional disturbances. The patient has multiple symptoms like palpitation, weakness, giddiness and often described

by the patient as shortness of breath, but if further questioned or demonstrated to the patient, it is sighing type of breathing, coming on at intervals. Clinical and radiological examination of heart is normal and electrocardiogram taken even during an attack of pain is entirely normal. These points are diagnostic of psycho-somatic pain and it should be diagnosed irrespective of whether there is an organic heart disease like rheumatic, coronary or hypertensive. Patients with other manifest hysterical symptoms and signs, sometimes complain of pain in praecordium which is frequently acute and severe, patient often screaming loudly. The severest pain that I have seen has been a hysterical pain in a young female patient, having also off and on hysterical fits and with a long history of psychic trauma.

I am quite conscious of the difficulties of diagnosing the cause of praecordial pain in extra cardiac group and sometimes it is impossible, but in nearly all cases, it is possible to give a definite opinion whether it is a cardiac pain or it is not. A confident reassurance that your heart is entirely normal is the first important step in his recovery and so often half of his symptoms are soon relieved.

You are well conversant with the clinical features of pain of cardiac ischaemia or cardiac infarct. The classic clinical description of anginal pain by William Heberden, written as long back as 1772, is enough to diagnose large majority of cases of angina pectoris or cardiac ischaemia. I need only emphasise a few points viz its location, its character, its relation to effort and relief by rest and nitrites. It is located in the substernal region anywhere from the epigastrium to the root of the neck just to the left of the sternum less frequently over the praecordium and rarely at the apex of the heart. The patient complains of a peculiar distress in the chest described as a disagreeable feeling, a sense of tightness or constriction or choking or indigestion or a feeling of fullness but never a lancinating or pricking or stabbing type of pain. Walking is the most important form of physical effort to precipitate an attack, particularly if executed quickly or uphill. Full meals, cold weather and emotional upset are important predisposing factors. To relieve this distress patient prefers to remain still standing or may continue to walk slowly if the attack is not severe or the journey not uphill. When the pain recurs under the same condition from day to day makes practically certain the diagnosis of ischaemic pain. If a person suffering from ischaemic pain happens to be young or a female patient always think of predisposing causes like hypertension, anaemia, diabetes, aortic valvular disease, syphilitic aortitis, myxoedema, paroxysmal tachycardia, severe mitral stenosis, coronary emboli or aberrant coronary artery. Although normal bloodpressure is common among males with angina, hypertension is the most important predisposing factor in females. Despite the great dependence on the subjective symptoms, the diagnosis of cardiac ischaemia by and large can be made with a high degree of accuracy. In any case where there is a doubt, electrocardiogram is very helpful. S T segment and T wave changes or presence of pathological Q wave are frequent findings. In the cases seen by me a very high percentage show pathologic ECG changes, which though in no way specific, are helpful in avoiding the error of making a diagnosis of normal heart and in a suspected case, the myocardial damage is highly likely to be due to cardiac ischaemia. If ECG taken at rest is within normal limits of

physiological variations, it should be taken after an exercise Test and if it is still found normal the diagnosis should be revised unless there is a very strong clinical suspicion. Deep but narrow Q wave and T wave inversion in L_3 and left axis deviation are not uncommonly found in obese individuals and in abdominal distension with high diaphragms and horizontal lie of the heart and do not by themselves denote any myocardial damage. Q_3 should be considered abnormal if it is 0.4 sec or more wide, when it is about 50 per cent or more the amplitude of the tallest R in the standard leads and Q_2 is about 25 per cent the amplitude of R_2 . Presence of abnormal Q wave in the left leg unipolar lead (AVF) is highly significant, denoting evidence of old posterior myocardial infarct. Unipolar limb lead Electrocardiography will help in deciding the position of the heart.

Another common cardiac symptom is dyspnoea or breathlessness. As breathlessness is the primary complaint in heart failure, the patient or the doctor quickly suspects heart as the cause. But it must not be forgotten that there are other causes of shortness of breath.

Obesity itself in an otherwise healthy individual can produce shortness of breath which is not progressive and is apt to be elicited only on effort, particularly climbing of stairs. With advancing age, especially in the presence of obesity, particularly involving the abdominal region, this natural reaction to increased physical performance is expected. The diaphragm does not descend as readily and is apt to be held in a high position and the vital capacity of the lungs is diminished. It follows therefore that not all obese patients who have dyspnoea, have heart failure and that even where there is definite evidence of organic heart disease, the dyspnoea may be only partly, if at all, the result of heart disease. The presence of horizontal position of the heart, giving an impression on radioscopy of apparent enlargement of the heart and left axis deviation with presence of Q wave and T_3 inversion in L_3 make the mistake all the more likely. It is quite likely that some of these obese patients are being treated for heart disease when I feel that they have nothing more than obesity. Before one pronounces that there is radiological enlargement of the left ventricle, the patient should be screened during inspiration in postero-anterior view and in left oblique position and one must satisfy the following criteria *viz* (1) Rounding of the left ventricular contour, particularly in its upper portion, (2) increase in the length of the left ventricular segment with elongation downward and (3) posterior bulge seen in left anterior oblique position. Left axis deviation by itself does not mean left ventricular hypertrophy and all the ECG changes noted above are commonly found in obese patients, because of the horizontal lie of the heart. To diagnose left ventricular hypertrophy, there must be ST depression and T wave biphasic or inverted in L_1 and in chest leads on left of the precordium (e.g. V_1 and V_6). The QR interval may widen. Remember that the earliest evidence of left ventricular hypertrophy is radiological, obtained on fluoroscopic examination of heart in P.A. and anterior oblique positions and not Electrocardiographic. ECG may be completely normal.

Allergic bronchitis, Tropical Eosinophilia and Bronchiectasis are not uncommon associations, with organic heart disease, as partly or wholly responsible for the cause of cough and dyspnoea. When a

patient is referred for cough and dyspnoea with organic heart disease, these symptoms have been interpreted as cardiac dyspnoea or cardiac asthma. A male patient aged 58 had attacks of cough with dyspnoea. More than a year back, he had coronary thrombosis. He was thought to be in a serious state of cardiac asthma with a bad prognosis. Clinical examination of heart did not reveal any abnormality and heart size was also normal. Expiration was prolonged with rhonchi all over chest and there was notable absence of basal rales. ECG showed old and healed anterior myocardial infarct. In view of the absence of dyspnoea in between the attacks, lying comfortably flat with one pillow, presence of expiration prolonged with rhonchi and absence of basal congestion, it was thought that bronchial or broncho-pulmonary factor seemed very important. There was polymorpho-nuclear leucocytosis with eosinophilia and dramatic improvement and complete recovery from cough and dyspnoea on administration of arsenicals. After a year's follow up, he is quite well. This illustrates that patient was suffering from Tropical Eosinophilia and left sided heart failure was not responsible for dyspnoea and cough. I have also come across cases of mitral stenosis admitted for attacks of dyspnoea and cough which can be mistaken as congestive cardiac failure but on proper examination and followup and after excluding conditions like paroxysmal auricular fibrillation or paroxysmal tachycardia responsible for acute failure in mitral stenosis they had an associated condition of allergic bronchitis or Tropical Eosinophilia, partly or wholly responsible for dyspnoea.

In old people with arteriosclerosis having blood pressure of the variety of 160—180 mm Hg systolic and 80—100 mm Hg diastolic, chronic bronchitis or bronchiectasis and emphysema are common associations. The dyspnoea is attributed to hypertensive failure when I am convinced that some of these have bronchopulmonary affections responsible for dyspnoea. This is important because the prognosis, management and treatment are very much different.

I have already pointed out to you the frequent presence of sighing type of breathing in patients having infra-mammary psychosomatic pain. It is a common experience that whenever we are relieved of tense or anxious situation, we take a sigh of relief. It is quite possible that periodic sighing respiration may be an expression of relief from chronically anxious and tense state of mind which may be present at a sub-conscious level. Whatever it may be, it is one of the pathognomonic signs of psychoneurosis and though described by the patient as dyspnoea there is no increase in respiration rate and it should not be taken at its face value but either shown to the patient or asked the patient what he or she means by it.

Hysterical dyspnoea with respiratory rate increased to about 40—60 per minute is not uncommonly seen in young female patients having other manifest symptoms and signs of hysteria. Absence of signs in the lungs and lying flat undisturbed for long, though seemingly in a serious state of dyspnoea, are important findings. Pain in praecordium, rapid respiration rate and irregular pulse because of marked sinus arrhythmia mimicking auricular fibrillation, were the findings met with in a young girl, referred as a heart attack, but clear chest, regular pulse on asking the patient to stop breathing, the presence of associated hysterical manifestations and proper follow up, decided beyond doubt.

the diagnosis as hysterical pain, hysterical dyspnoea and marked sinus arrhythmia in view of rapid respirations

Oedema over ankles and legs is one of the important signs in right sided failure. Heavy persons who have to stand for long in one position are likely to have slight oedema over the ankles. The presence of varicose veins favours its occurrence. Obstruction of the venous circulation is frequently responsible for oedema. Before you diagnose cardiac oedema, make sure that venous pressure is raised and liver is enlarged and tender. If these are not present, look out for local cause of oedema viz venous thrombosis, varicose veins, tight garters etc. Hypoproteinaemia as a cause of oedema should be kept in mind even in patients having an organic heart disease. Malnutrition is so rampant in our country that hypoproteinaemia as a cause of oedema is very frequent in hospital type of patients. A young girl, primipara, running 7th month of pregnancy, was referred for advice as to termination of pregnancy as she was supposed to be suffering from congestive cardiac failure because of oedema over legs and loud systolic murmur at mitral area. In view of absence of pulmonary congestion, venous pressure not raised, and liver not enlarged and tender, congestive cardiac failure due to mitral disease was ruled out. She had hypoproteinaemia and anaemia as the cause of oedema and the murmur was not due to mitral disease but it was a late systolic innocent murmur—Grade III. She had a normal delivery and after a year's follow up, she is none the worse for that noise with a reassurance that she can live as normally as any other normal person. To quote Paul White "Much digitalis has been wastefully prescribed in such cases before careful appraisal of the heart itself has demonstrated its futility."

Hypertension—Elevation of the systolic element of the blood pressure without concomitant rise in the diastolic element is so common in old people that the blood pressure of 160/80-100 mm Hg is a frequent finding. It is being often told to the patient that you are suffering from slight high blood pressure. The word "high blood pressure" is such a dread in public mind that once the idea of blood pressure is put in his mind, he becomes so manometer-minded that small rises of blood pressure give rise to an anxiety, ultimately leading to neurosis. Systolic hypertension is either due to an increase in the cardiac output or to a greater rigidity of the larger vessels of the arterial tree. It is not a consequence of increased peripheral resistance. This type of systolic hypertension is met with in aortic insufficiency, hyperthyroidism, arterio-venous communications, heart-block with slow-rates and sclerosis of the aorta and larger vessels. If in aortic insufficiency or thyrotoxicosis or heart block, patient is not told that he has hypertension, why mention the same to patients having arteriosclerosis in which also systolic rise of blood pressure is compensatory? I feel that the mention of high blood pressure should be omitted in such cases unless there is clinical, radiological or electrocardiographic evidence of left ventricular hypertrophy, and the patient told that your vessels are a little aged or the doctor told that he has arteriosclerosis. I am putting this proviso because in some cases, I have found systolic blood pressure round about 200 and diastolic about 80-95 associated with left ventricular-hypertrophy. I am pleading this because systolic rise of blood pressure in old people without concomitant rise of diastolic pressure is so benign

that patients do not suffer from complications like left ventricular failure attributable to hypertension but live a long and useful life unless vascular complications because of athero-sclerosis supervene

There are many other problems *e g* systolic murmur at mitral area which is frequently mistaken as mitral disease, healthy splitting of 1st sound as presystolic murmur of mitral stenosis or triple rhythm, displaced apex beat as enlarged heart especially in cases of depressed sternum and T₁ inversion because of wrong connections interpreted as evidence of myocardial damage or coronary disease. It is difficult to discuss them in such a short space of time however much I may like it. I shall only conclude by saying that a good fluoroscopic and electrocardiographic examination is a valuable aid, but with the bewildering growth of specialised examinations for precision in diagnosis, a discriminative and a good bedside clinical examination becomes all the more important

APPENDICITIS

By
Dr V M KAKKINTI M.A., M.B., F.R.C.S.

The lesions of the appendix are of many types, many more than are usually described in the text books and vary from the mild type of inflammation usually treated as chronic dyspepsia to the more severe type of gangrenous and fulminating type of appendicitis.

The congenital factor should be taken into consideration in the etiology of appendicitis. A congenitally very long or short appendix or one with an ill developed Gerlach valve in its structure may become pathological than a normal appendix. A congenital malformation is an important etiological factor.

In acute appendicitis fever is invariably present. But in the case of Wilkie, in the acute obstructive type there is no rise in temperature. The pulse during the first six to twelve hours. In the acute type, the initial pain no doubt is in the umbilical region. But later it localises itself in the right iliac fossa.

According to Steinberg chronic appendicitis is of two types, inflammatory and non-inflammatory (retrogressive or degenerative). The first he calls regular appendicitis and the second irregular. In the second type the symptoms are very mild, pain is always localised in the right iliac fossa and fever, leucocytosis etc. are not present. The other types of chronic appendicitis are the atrophic type, the exudative type, the interstitial type, and the obliterative type.

Von Hausemann describes another type which he calls mucous cystic bulosis, in which a sort of mucous cyst is formed at the distal end of the appendix by a chronic inflammatory process. In some cases the rupture of this cyst may cause the gelatinous fluid which is set free to give rise to symptoms of acute abdomen.

As regards treatment operation is the treatment of choice when appendicitis is diagnosed. One does not know when a mild case of appendicitis may develop into an acute attack. Moreover even if an acute attack does not develop operation will save the patient from chronic ill health due to the appendicular lesion.

In the author's experience the expectant line of treatment operated on after the acute attack has subsided gives the best results. He has followed this method and he has been gratified by the result. Out of about 900 cases of appendicitis that he operated he had three deaths. Two of them occurred in acute cases which were operated on by him soon after admission in the acute stage. The third death occurred in a patient with chronic appendicitis on the twentieth day after operation with symptoms of acute intestinal obstruction. In two cases in which the patients had severe acute attack of appendicitis and were operated on in the quiescent period, on opening the abdomen there was found evidence of gangrene and perforation which had occurred during the acute attack, but which did not lead to any disaster as the expectant line of treatment was strictly followed.

Summary of the paper read before the 90th meeting of the South Indian Medical Staff Society held on Saturday, the 10th September 1916.

Critical Notes and Abstracts

ANDROGEN THERAPY—W O THOMPSON, M D , Chicago, *Annals of Internal Medicine*, January 1949, 34 55-68

Androgens are general metabolic stimulants and not merely substances which affect sex function. This is emphasized by the variety of the secondary sex characteristics, all of which owe their development to the action of the male sex hormone. This substance is responsible for growth of the external genitalia, increase in the size and firmness of muscles, normal configuration of the skeleton, growth and function of the prostate, masculine distribution of hair, normal emotional reactions, and lowering of the pitch of the voice.

There is debate as to what the male sex hormone is, but testosterone is the most potent androgenic material isolated, and many consider the hormone to be this substance in chemical combination. In order to carry out androgen therapy intelligently, a clear understanding of the various types of hypogonadism is necessary.

The testis has two functioning parts, namely, the seminiferous tubules which produce spermatozoa, and the interstitial cells which produce male sex hormone. The functions of these two portions of the testis are inter-related and normal spermatogenesis appears to be in part dependent on normal production of the male hormone. The testis may show atrophy of the seminiferous tubules, however, without much impairment of function of the interstitial cells.

There is a close relation between the anterior lobe of the pituitary and the testis. The former produces a follicle stimulating hormone which influences the function of the seminiferous tubules, and a luteinizing hormone which stimulates the interstitial cells to produce male sex hormone. Hypogonadism may therefore be either primary or secondary, the primary type being caused by some defect in the testis itself, and the secondary type resulting from some defect in the stimulating mechanism of the pituitary.

Androgen therapy is substitution therapy, whereas gonadotropic therapy is stimulation therapy. In general, androgens should be employed when it is impossible to stimulate the testis adequately with gonadotropins. Chorionic gonadotropin is very effective in stimulating the interstitial cells of the testis, but we lack a satisfactory method of stimulating spermatogenesis. Nonetheless, the substances available are of use in a wide variety of conditions.

In eunuchism, there is complete loss of both functions of the testes as a result of the removal, injury or atrophy of these glands. The administration of testosterone propionate usually substitutes completely for the male sex hormone. The ideal age to begin treatment is 11 or 12 years. If given at this time, testosterone will cause normal development of the secondary sex characteristics. If treatment is delayed until after puberty, some skeletal disproportion will persist, and the genitalia, musculature and hair will not develop fully. When men as castrated after puberty, the administration of testosterone propionate will restore the secondary sex characteristics to normal. In all these individuals, the defect is a permanent one and treatment is necessary throughout life. The amount of material required to produce maximum development varies in individuals, but 250 mg intra muscularly 3 times a

week is the dose for many. In some, as much as 50 mg a day may be necessary.

In some cases of cryptorchism, the testes will descend into the scrotum with glandular therapy but very often surgical measures are necessary, the cryptorchism may be due to endocrine or mechanical factors. When testes are in the abdominal cavity they should be brought into the scrotum as early as possible. The risk of permanent damage to them is greater the longer they remain in an abnormal environment. Chorionic gonadotropin is the best therapeutic agent and the intramuscular injection of 500 I U 3 times a week should be tried first. If ineffective, testosterone should also be used. After the testes have been brought into the scrotum, the need for further therapy must be determined at puberty.

In eunuchoidism, the testes may be atrophic and in the scrotum or there may be bilateral cryptorchism. In this condition, there is only partial loss of testicular function. There is always a deficient production of male sex hormone and almost always a deficiency in spermatogenesis. It is important to determine if the testicular defect is primary or secondary and to treat the patient accordingly. If normal amounts of follicle stimulating hormone can be demonstrated in the urine, the defect is primary. If facilities for hormone assays are not available the type of eunuchoidism may be determined by administration of chorionic gonadotropin. If the testes responds to this therapy, the defect is secondary.

The treatment of the eunuchoid state should be started at 11 or 12 years of age. In these persons, the testes are often abnormally small, but is not easy to be certain that testicular function is deficient. For this reason, treatment is often delayed until irreparable changes in the skeleton and musculature occur. If eunuchoidism is treated after puberty, the testes may not produce enough male sex hormone to cause adequate development of the secondary sex characteristics. In this situation, treatment with testosterone propionate in the dose mentioned may be desirable though the eunuchoidism is of the secondary type. Chorionic gonadotropin may produce genital growth when the testes are in the abdomen but stimulation therapy may be more effective if the testes are in the scrotum.

In pituitary dwarfs, hypogonadism is of the secondary type and chorionic gonadotropin is usually effective in stimulating skeletal growth. Testosterone needs to be used only when a maximum effect cannot be obtained with stimulation therapy. Treatment should be started at about the age of 12 years, and when begun at this time, therapy causes the patient to grow taller and to develop normal proportions. He remains a dwarf, however, as he is without the benefit of pituitary growth factor of which we have no effective preparation. In older pituitary dwarfs, the testis does not respond well to stimulation, and testosterone is indicated.

In patients with inoperable carcinoma of the breast, 100 mg of testosterone propionate 3 times a week ameliorates unpleasant symptoms. It does not have much effect on the breast lesion, but some calcification may occur in bony metastases, pain may be relieved, and the nutritional status of the patient improved. This type of therapy is valuable in pre-menopausal patients when estrogens are said to be contraindicated. High doses are maintained for 8 to 10 weeks, following

attacks of cardiac asthma were also relieved. In all cases of this type it is reasonable to assume that the collateral coronary circulation was improved.

It is concluded that khellin is an effective drug for the continuous treatment of angina pectoris and also for the individual attacks of pain. Suggested oral dose of the drug is 50 to 100 mg three times daily, by intramuscular injection, 100 to 200 mg may be given. A few patients complain of a sensation of warmth and mild dyspeptic symptoms or insomnia, but the side effects are few and the bleeding and coagulation times are not altered. The action of khellin, in general, is similar to that of aminophyllin but is approximately four times stronger.

THE NEWER ANALGESIC DRUGS THEIR USE AND ABUSE

—HARRIS ISBELL, M.D. Lexington, Kentucky *Annals of Internal Medicine*, December, 29, 1949 1003-1013

A constant search has been carried on for drugs which would be equal to morphine in analgesic action but which would have fewer side effects, and particularly for drugs which would have less addiction liability. Little progress was made until 1939 when Small, Eddy, Mosettig, and Himmelsbach issued a summary of their studies on methyl dihydro-morphinone, or metopon, a new member of the morphine series of drugs which appeared to possess some distinct advantages over morphine. Since 1939, two new potent analgesic drugs, which are not chemically related to morphine or to each other, have been discovered. These are meperidine, or demerol (ethyl 1-methyl-4-phenyl-piperidine-4-carboxylate), and methadon, or amidone (6 dimethylamino-4-4-diphenyl-3-heptanone). The fact that, despite the lack of chemical resemblance, meperidine and metopon have much in common pharmacologically with each other and with morphine is rather astonishing and has given great impetus to the search for more effective analgesics. We can expect the development of new compounds in the meperidine and methadon series which may possess advantages over the original drugs, and other analgesic drugs with molecular structures differing from any yet known may be discovered. While this quest for new substances with pain-relieving actions is desirable, it will also bring confusion. The choice of an analgesic drug may soon be as complex as the choice of an hypnotic drug. It therefore seems wise at this point to attempt to assess the advantages of the three new analgesics, metopon, meperidine, and methadon, to consider their addiction liability, and to describe or discuss some indications for their use.

Analgesic Effect—Morphine and metopon are the two most effective drugs in altering all factors concerned with production of analgesia following a single dose. Meperidine and methadon are less effective. However, if the drugs are used every four to six hours, the order is radically altered, methadon is slow acting, cumulative drug and, when repeatedly administered, it exerts an effect on the reaction to pain equal to that produced by morphine and excels morphine in sedative and hypnotic effect. Methadon is, therefore, not a good drug for pre-anesthetic medication and is only fairly effective in situations requiring very rapid relief of pain, but it is a very good drug for the relief of chronic pain. Under conditions of repeated dosage, methadon is equal to morphine and metopon in inducing analgesia. Meperidine, though fairly effective, is not as reliable or as potent an analgesic as are the other three drugs.

METOPON In minimal analgesic doses, metopon is less likely to produce sedation and mental dullness than is morphine. Metopon, in conjunction with inhalation anesthetics, may produce serious respiratory depression, and is, therefore, contraindicated as pre-anesthetic medication. Metopon is almost as effective in relieving pain when given by mouth as when administered hypodermically. Due to difficulties in manufacture, metopon is about 10 times as expensive as morphine, and the amount available for use may always be limited.

MEPERDINE It is common clinical experience that persons who cannot tolerate morphine because of nausea may tolerate meperidine. In man, meperidine relaxes spasm of the smooth muscle of the gastrointestinal tract and the ureter. Although the role of the spasmolytic action of meperidine in relieving colicky pain has been over-emphasized the drug at least does not increase spasm of smooth muscle as does morphine. Meperidine does not produce constipation. It is effective when administered by mouth, but is more expensive than morphine.

METHADON Methadon is very similar to morphine in all its pharmacologic actions. It depresses respiration as much as does morphine, causes nausea and vomiting just as frequently, and is constipating. It is quite irritating when injected subcutaneously and, if injected repeatedly into the same sites, causes severe inflammation and induration of the skin. Nausea and vomiting of the skin. Nausea and vomiting occur so frequently after oral administration that the drug cannot be used by this route.

Addiction Liability.—Tolerance to the clinical analgesic effects of metopon, methadon, and meperidine develops more slowly than does tolerance to the analgesic effect of morphine. The slow development of tolerance is the greatest advantage these drugs possess over morphine. Metopon has one further advantage, tolerance to the clinical analgesic effect of metopon is abolished by withdrawing the drug for only 8 to 14 hours. This rapid loss of tolerance has not been shown to occur with any other analgesic drug.

Metopon, meperidine, and methadon all have physical dependence liability. However, abstinence symptoms following withdrawal from both meperidine and metopon came on more rapidly, were less intense, and subsided more rapidly than did abstinence symptoms following withdrawal from morphine. The abstinence syndrome following withdrawal of methadon was milder than the abstinence syndrome following withdrawal of metopon or meperidine. Following withdrawal of methadon, very few of the autonomic signs so characteristic of the abstinence syndrome following withdrawal from morphine, metopon, or meperidine were observed.

The evidence forces us to conclude that all three drugs are addicting. Any differences noted in the addiction liability of the new analgesic drugs from that of morphine are differences in degree, not kind. Tolerance has developed to actions of all three drugs. Physical dependence has been demonstrated after prolonged administration of all three drugs and, more important, all three drugs have been shown to possess considerable habituation liability.

Clinical Applications of the New Analgesics —It is not to be expected that these new drugs will completely replace morphine. Due to its quick but long-lasting action, its reliability, its powerful sedative action,

and its relative cheapness, morphine is still the choice for most patients requiring relief of pain for periods of less than 14 days

The use of metopon has been restricted by the National Research Council to persons with chronic painful diseases, and the drug is available for oral use only

Meperidine seems to have lost popularity because it is not as reliable or as long-lasting an analgesic as is morphine or methadon. Severe grades of pain are often not well controlled with meperidine. The drug, however, deserves a trial in cases of pain associated with spasm of smooth muscle. It is also indicated for persons who are nauseated by morphine. Since it is effective orally, and since tolerance develops slowly, it is quite useful in managing chronic diseases associated with mild grades of pain.

Methadon can be used in most situations where morphine is indicated. Due to its slow cumulative action, it is probably not as desirable as morphine in situations demanding very quick relief of pain. The drug is useful in chronic diseases since tolerance develops slowly and physical dependence on the compound is quite mild. If a person with a chronic disease has received morphine for a long period of time, methadon is the only drug which can be satisfactorily substituted for the morphine, since meperidine and metopon do not completely suppress signs of the abstinence syndrome following withdrawal from morphine. The fact that methadon cannot be used orally is a great disadvantage, which largely limits its use to cases under hospital supervision. Due to the low intensity of the abstinence syndrome following withdrawal of the methadon after substitution for morphine in cases strongly addicted to morphine, methadon is the drug of choice for treatment of the morphine abstinence syndrome.

Prevention of abuse of the new Analgesic drugs —Meperidine, metopon and methadon have been placed under the provisions of the Harrison Narcotic Act in order to minimize abuse of the drugs and to limit the spread of addiction to them. Physicians should keep the danger of addiction to three substances in mind and should exercise the same caution in prescribing them as is followed in prescribing morphine. The drugs should never be used when other drugs or other measures will suffice. The dosage should be held to the minimum compatible with adequate pain relief and the interval between doses should be as great as possible. The drugs should be discontinued as soon as the need for pain relief has passed. They should never be used primarily for their sedative actions. In chronic cases, they should be administered orally whenever possible. Self medication with a needle should be discouraged. The drugs should never be given intravenously, since this method produces maximum euphoria and carries a great risk of addiction. The drugs should not be administered to persons with known psychopathic or psychoneurotic personalities unless very definite indications for the use of a potent analgesic are present. The drugs should never be used for the relief of symptoms due to alcoholic excess since alcoholics are very prone to addiction. The drugs should never be used for the treatment of asthma, since asthmatics are also very susceptible to addiction. It is significant that several of the cases of primary addiction to meperidine observed in Lexington, Ky., became addicted as a result of administration of meperidine for the relief of asthma.

DERIVATIVES OF THE HYPOTHALAMUS IN THE HUMAN BRAIN

Topography, structure, and fibre connections of the nuclei comprising the derivatives of the hypothalamus in the human brain are discussed by the authors on the basis of comparative and ontogenetic evidence. During mammalian and human ontogenetic development, the primordial longitudinal hypothalamic cell zone gives origin to a dorsal and entopenduncular groups of nuclei, and to anterior, middle, and posterior groups. The dorsal and entopenduncular group, usually not included within the conventional definition of the hypothalamus, comprises the globus pallidus and the nucleus subthalamicus of Luys in addition to other structures.

This group is especially related to the extrapyramidal motor system, but is also closely connected with the conventional hypothalamic groups. The anterior, middle and posterior hypothalamic nuclear groups comprise the centres commonly designated as hypothalamic and may also be termed the hypothalamus sensu stricto. These centers are especially related to the autonomic nervous system. The anterior hypothalamic group includes the preoptic region, which is clearly a part of the diencephalon and not of the telencephalon impar, as frequently stated in the literature.

Functionally, the more anterior part of the hypothalamus seems to be concerned with parasympathetic outflow and the more posterior part with sympathetic outflow. The hypothalamus represents an important center for the regulation of body temperature and water balance. It is also implicated in the control of fat metabolism, sex functions, and sleep-wakefulness rhythm, and exerts an influence on carbohydrate metabolism. The hypothalamus is furthermore a significant link in the mechanism of emotional reactions.

(Kuhlenbeck, Hartwig and Haymaker Webb. "The Derivatives of the Hypothalamus in the Human Brain. Their Relation to the Extrapyramidal and Autonomic Systems." *The Military Surgeon* 105: 20-52 July 1949).

USE OF INTRAVENOUS QUINIDINE DURING CLINICAL ANESTHESIA FOR TREATMENT OF ACUTE ARRHYTHMIAS

Collins points out that quinidine preparations have been found effective clinically in treating disorders of cardiac rhythm occurring during anesthesia especially with cyclopropane. A highly soluble salt, quinidine lactate, has been tested and found to possess the same activity as the sulfate salt.

Originally, it appeared from clinical observation that quinidine administered intravenously was effective in about 10 to 12 minutes. However, examination of the electrocardiographic tracings reveals that many rhythms are reverted to normal in four to six minutes. Frequently a tachycardia, similar to the paradoxical tachycardia following the slowing of an auricular fibrillation, develops and lasts for one to three minutes.

No untoward cardiovascular reactions have been noted at the time of administration, and in fact there has been improvement with elevation of the systolic blood pressure. Neither has respiratory depression or bronchospasm been seen in the cases treated. No instances of idiosyn-

crazy have been detected in a careful post-operative follow-up. The use of quinidine, particularly its intravenous administration, has been avoided by many physicians because of its reputed marked toxicity. Much of this feeling has apparently developed on theoretic grounds, especially in relation to patients with chronic auricular fibrillation.

The most feared reaction is that of embolism. For this to happen auricular fibrillation must have existed for some time in order that a thrombus form. Stroud and Laplace state that the incidence of embolic phenomenon in chronic auricular fibrillation is no greater with quinidine than with digitalis. Marvin reports that embolic episodes are definitely less when quinidine is used than when no drug is administered. Likewise the report by McMillan in which patients with chronic auricular fibrillation were treated with quinidine shows that serious side reactions to quinidine are few.

In other words, it appears that toxic reactions to quinidine have actually been overrated and a useful drug has been neglected. Furthermore, the arrhythmias developing during anesthesia are acute, and hence thrombus formation is minimal or unlikely. The precipitation of ventricular fibrillation by quinidine is a possible hazard. However, quinidine is actually indicated for breaking the mechanism of paroxysmal ventricular fibrillation.

(Collins, Vincent J. New York, N. Y. "Use of Intravenous Quinidine During Clinical Anesthesia for Treatment of Acute Arrhythmias." *New York State Journal of Medicine* 49: 1554-1555 July, 1949)

ENDOCARDITIS IN "MAIN LINE" OPIUM ADDICTS

Eleven instances of endocarditis in opium addicts who used the intravenous route of administration were recorded in a three-year period by Luttgens. Interference with the supply of opium from the Middle East and the Far East during the recent war resulted in the importation of a crude opium from Mexico. It has been suggested that in the handling of the crude material without precautions as to sterility, bacteria gain entrance to the blood stream and give rise to endocarditis.

The causative organism in seven of the 11 cases was a non-hemolytic type of streptococcus, resistant to penicillin. In one of these cases, a species of *Candida* also was present. *Esch. coli* was responsible in one case, no organism was isolated in another. The aortic valve was involved in these nine cases, involvement of the mitral valve, when present, appeared secondary. Streptomycin effected a cure in one case of endocarditis caused by *A. aeogenes*. The mitral valve was probably involved in this case.

In one case a patient who had tricuspid endocarditis caused by *Ps. aeruginosa* survived for five months, despite only transient improvement resulting from streptomycin therapy. No definite evidence of rheumatic, congenital or syphilitic heart disease was present in these cases. It is possible that in the particular type of endocarditis concerned the heart valves need not have been damaged previously and that normal valves may have become infected after repeated exposure to injected bacteria.

(Luttgens, William F., San Francisco, California. "Endocarditis in 'Main Line' Opium Addicts." *Archives of Internal Medicine*, 83: 685-684 June, 1949)

IRON OVERLOAD (HEMOSIDEROSIS) AGGRAVATED BY BLOOD TRANSFUSIONS

The authors report five cases of iron overload (hemosiderosis) aggravated by blood transfusions on which autopsies were subsequently performed. The five cases include three definite types of anemia. There were two instances of acquired hemolytic anemia that failed to respond to splenectomy. In two cases the picture of "aplastic anemia" was present. One patient had a definite pulmonary fungus granuloma demonstrated by tissue sections, and the other patient had a tuberculoid granulomatous nephropathy and was found to have widespread fungus overgrowth 24 hours after death.

Whether the latter constituted an agonal invasion related to the renal granuloma could not be decided. The fifth case was one of classic pernicious anemia with repeated relapses due to failure of the patient to maintain liver therapy. Widespread tissue damage was noted, and factors which may account for this are discussed by the authors.

The outlook for patients that are sustained hematologically by prolonged blood transfusion therapy does not appear good. Two complications seem likely to develop: (a) frequent reactions to the infused blood, with a more rapid dissipation of the infused erythrocytes and (b) iron overload of body tissue, mainly the liver.

(Mulhhead E E, Dallas, Tex et al. Iron Overload (Hemosiderosis) Aggravated by Blood Transfusions. *Archives of Internal Medicine*, 83: 477-501 May, 1949)

SEX-HORMONE RELATIONSHIPS IN MEN

Hoskins and Pincus report data on the steroid components of the urine of male schizophrenics as well as of normal men and women. Groups of 23 normal men, 11 normal women, and 29 schizophrenic men were compared as to the urinary output of androgen, of estrogen, and of 17-ketosteroids. The ratios of these substances to each other were calculated for each of the three groups.

There was considerable overlapping in the various categories but the women were found to have excreted more estrogen and less androgen and 17-ketosteroids than did the men, the differences in the means being statistically valid. The androgen-estrogen ratio in the men surpassed that in the women in proportion of 16.8 to 2.8. The proportion of active androgen in the total ketosteroid output was also higher in the normal men than in the women.

In case of the patients (men) the total estrogen output was lower than that of the women in proportion of 15.8 to 26.8 whereas it was slightly but significantly higher (15.8 to 12.6) than that of the normal men. The androgen output of the patients surpassed that of the women in proportion of about 12 to 7 but fell significantly below that of the normal men by a ratio of 12 to 18. The mean androgen-estrogen ratios in the women were 2.8, in the men 16.8, and in the patients the intermediate ratio of 9.7.

In all these various hormonal categories, therefore, the schizophrenic men showed a definite approach toward the feminine patterns but remained more "masculine" than the normal women. As regards psychologic characteristics the five patients with the lowest androgen-to-estrogen ratios were less aggressive than the four with the highest

ratios. Such homosexuality as was evident was also a matter of more active concern in the latter group.

(Hoskins R. G. Worcester State Hospital Mass and Pineus Gregory: Sex Hormone Relationships in Schizophrenic Men *Psychosomatic Medicine* 102 100, March April, 1949)

HEARING REEDUCATION

According to Browd auditory reeducation is an effective therapeutic measure indicated in all degrees and patterns of hearing loss of long standing and in all situations in which an untroublesome level of hearing has not been, or is not likely to be reached or maintained through other measures. Though generally thought to be a procedure which can be given only with a hearing aid, auditory reeducation may be given effectively with or without a hearing aid.

On the other hand, a hearing aid seldom provides a satisfactory level of hearing without auditory reeducation. As a rule, those with more than a 40 decibel average loss between the frequencies of 128 and 8192 cycles per second in the better ear require both hearing aid and hearing reeducation, but some patients with a loss as great as 50 decibels can be brought to a satisfactory level without a hearing aid. Generally, those with less than a 40 decibel average loss between 128 and 9182 in the better ear can attain a satisfactory level of hearing through auditory reeducation without a hearing aid, but some require both hearing aid and hearing reeducation.

Patients with a 20 to 35 decibel loss in the better ear can tolerate a hearing aid in very few situations in the course of the day. On that account, they have in the past been forced to remain hard of hearing, although numerically they constitute an appreciable portion of the hard of hearing group. When given auditory reeducation alone few of them fail to attain a satisfactory level of hearing. Hearing reeducation without a hearing aid is also indicated for the following persons:

1. Those with a 35 to 50 decibel loss in the better ear who are acoustically suited, but whose station, calling or temperament makes them unsuited, for a hearing aid.

2. Those unsuited for a hearing aid whose tinnitus or other aural symptoms are caused by the hearing loss itself.

3. Those who have had a hearing aid fitted to their poorer ear because they were unable to tolerate a hearing-aid in the better ear. Such patients can attain a satisfactory level of hearing through auditory reeducation alone and thus are relieved of the necessity of resorting to a *gauche* procedure.

4. Those who are well suited but prefer not to wear a hearing aid. Unless they have more than a 50 decibel loss in the better ear it would be justifiable to give them auditory reeducation first and decide later whether they have to wear a hearing device.

5. Those, who through disuse of the poorer ear, exhibit one or more of the disabilities characteristic of monaural hearing.

(Dr. Victor L. Browd: 'Hearing Re-education Without the Use of Hearing Aids' *Archives of Otolaryngology* 49: 511-528 May 1949. Dr. Browd is connected with the Department of Otolaryngology, Mount Sinai Hospital, New York, New York.)

IRON METABOLISM AND HEMOCHROMATOSIS

Granick discusses iron metabolism and hemochromatosis. The review is divided into four parts. In part one he enumerates and classifies the iron compounds of the body. In the second part he

discusses the properties of some of these iron compounds. In the third part the properties and the hypotheses concerned with the regulation of iron absorption by the gastrointestinal mucosa is discussed, and in the last part, certain of the aspects of iron metabolism, as they might be related to hemochromatosis, is discussed.

To the practicing physician the practical question must be uppermost. What can be done for a patient with hemochromatosis? Little hope can be extended to a far-gone case except symptomatic treatment of cirrhosis, or the diabetes or heart involvement. However, there would seem to be already a rational approach to the prevention of hemochromatosis.

The hemochromatosis of the nutritional variety is probably extremely rare in this country. We are then concerned primarily with the hemochromatosis due to metabolic error.

1. Prevention and treatment depend on an early recognition of the development of this disease. A diagnostic sign is a rather high serum iron and an otherwise normal blood picture. If near relatives have had hemochromatosis there is all the more reason to be suspicious.

2. A diet might be considered which would limit iron absorption first by complexing the iron and secondly by keeping iron in the ferric state. A diet high in phosphates especially in phytic acid would render the ferric iron highly insoluble. One might consider increasing the oxidizing activity of the diet by adding vitamin K as the naphthoquinone. One might also decrease the intake of ascorbic acid in the food during meals to prevent the ferric iron of the food from being reduced.

3. One might consider the feasibility of making the potential hemochromatosis patient a regular blood donor since bleeding would be the only direct way of removing accumulations of iron from the body. In hemochromatosis developed to the stage of liver or pancreas involvement, however, this procedure might not be advisable.

4. An aim of the future would be to study the metabolism of the mucosal cell in order to understand the factors governing the reducing mechanisms of the cell. Eventually one might attempt to control this activity by blocking one or another enzyme with some enzyme inhibitor or anti-metabolite.

(Granick S. "Iron Metabolism and Hemochromatosis." *Bulletin of The New York Academy of Medicine* 25: 403-428 July 1949. Dr Granick is associated with The Rockefeller Institute for Medical Research New York New York)

Opinions and Diversions

The Year is Dying

*The year is dying ,
Our lives are passing
What do we think of that we have done ?
What do we long for round the corner ?
Where are we journeying ? And with what load ?—
Does the pathway matter ?
We cannot turn backward ,
We must go to the end whatever it be,
Into eternity briefly recorded,
Into oblivion all forgot
Nothing endures but the exquisite sky,
This limitless throne-room of God,
The flight of birds, the spumy leap of waves,
All Earth's untroubled bounty,
Wind on the hills, and morning hope,
Courage, and children's sudden laughter, and remembrance
Of great love shared
And kind deeds done —(GORELL, Poems, 1904-1987)*

Schemes and plans for health and education

It is said that Government of India spends about seventy per cent of its revenues on military expenses and so has little money for health or education ! Our governments, both central and provincial, with their top heavy bureaucracy and wasteful immature schemes can have but little money to spend on people's health and education For the rulers who professed a belief in non-violence and who fought against bureaucracy and heavy military expenses for thirty years this indeed is an embarrassing situation But our wise rulers know Wutzu's "The Book of War" (c 500 B C) where it is written —

"In ancient times, the Prince Chensang cultivated *virtue*, and put away military things, and his kingdom fell

"The Prince Yuhu put his trust in numbers, and delighted in war and was driven from the throne

"Therefore the enlightened ruler should ponder over these things , encourage *learning* and *virtue* in the kingdom, and be prepared against war from without "

Still, one likes to say with Shelley (*Hellas*, 1822) —

"Oh, cease ! must hate and death return ?

Cease ! must men kill and die ?

Cease ! drain not to its dregs the urn

Of bitter prophesy

The world is weary of the past,

Oh ! might it die or rest at last ! "

This age

"But, good God ! What an age is this, and what world is this ! that a man cannot live without playing the knave and dissimulation "—SAMUEL PEPYS

The poison of power

Nothing goes to the head like power. The effects of intoxicants are nothing compared to that of power. As the effect of intoxicating drugs varies according to the cerebral and cultural development of the subject, the results of power intoxication are also different in different individuals. The ignorant man with power is a most dangerous person in modern society. The psychopath with homicidal tendencies armed with a gun running amok does less harm than a psychopath armed with power and put in a responsible position where he can wield it without restraint or hindrance. Acton, a profound student of history, never tired of saying that power always corrupts a man and absolute power corrupts absolutely. When an unthinking minority, through force of circumstances, is placed in a position of power it does immense harm. It is immaterial whether this coercively controlling minority is composed of confirmed 'patriots', jailgoers, private capitalists or government bureaucrats, or of all classes of bosses acting in collaboration. The result of their coercive action remains the same—the growth of free society is curbed, viciated or perverted. The well-meaning—but drunken with power and hence deprived of reason—politician indulges in whims which spell ruin for the people. The rulers of Germany, 1931-1945, are examples of immature men who came to power and tried to put into practice their pet beliefs in astrology, homeopathy, race superiority etc and came to grief in time, but before that, like a bull in a China shop, turned the whole world topsy-turvy. When one thinks of the future of modern science and modern medicine in India, one wonders if our present rulers, both central and provincial, all excellent and honourable men, are also behaving or are going to behave in a somewhat similar irrational way. Otherwise how does one explain their various schemes for revival of dead and discarded systems of thought, waste of public money on personal whims, ayurvedic colleges, homeopathic university, university of nature cure, health centre to discover truth about various systems of healing, and what not? With one breath they talk of science, with other they run after mirage, practice magic, consult stars, and pray for miracles. The behaviour of these rulers adorning ministerial chairs is inexplicable except for the mechanization of "*some god of power to cloud their better sense*" (Aeschylus). The tolerant man feels with Rabbi Ben Ezra, (Robert Browning) —

*"Now, who shall arbitrate ?
Ten men love what I hate,
Shun what I follow, slight what I receive ,
Ten, who in ears and eyes
Match me , we all surmise,
They this thing, and I that
Whom shall my soul believe ? "*

And if there are rebuffs from the powers that be—

*"Then, welcome each rebuff
That turns earth's smoothness rough,
Each sting that bids, nor sit nor stand but go ! "*

Chaung Tzus has a good parable for these busybodies who think they can improve on nature, change science, work miracles, and bring

heaven on earth, by plans, schemes, laws, rules, ordinances, and if necessary, by shooting!

"The ruler of Southern Ocean was Shu, the ruler of the Northern Ocean was Hu, and the ruler of the Centre was Chaos. Shu and Hu were continually meeting in the land of Chaos, who treated them very well. They consulted together how they might repay his kindness, and said — 'Men all have several orifices for the purposes of seeing, hearing, eating, and breathing, while the ruler alone has not a single one. Let us try to make them for him! Accordingly they dug one orifice in him every day. At the end of seven days Chaos died.'"

If our Shus and Hus have their way and keep on digging holes in modern science and medicine it will not be long before the long-suffering Chaos (here alas! the people) is dead. "The Greeks believed that *hubris* was always followed by *nemesis*, that if you went too far you would get a knock on the head to remind you that the gods will not tolerate insolence on the part of mortal men"—(*Huxley*)

The Partition and Linguism

"So long as the arbitrarily delimited territories of Central America were called provinces of the Spanish colonial empire there was peace between their inhabitants. But early in the nineteenth century the various administrative districts of the Spanish empire broke from their allegiance to the "mother country" and decided to become nations on the European model. Result they immediately went to war with one another. Why? Because, by definition, a sovereign national state is an organization that has the right and duty to coerce its members to steal and kill on the largest possible scale"—(*Huxley*)

Medical News and Notes

MALARIA

An army of 8,000 men, using weapons ranging from airplanes to test tubes, has turned the Italian island of Sardinia into a battle ground for the war against malaria.

Back in 1945, the island was divided into more than 5,000 sectors by the Italian Government, in co operation with UNRRA and the American Rockefeller Foundation, opened its campaign against malaria-bearing mosquitoes.

Today, mosquitoes have disappeared from all but 3 of the sectors. As soon as mosquitoes are reported in any part of Sardinia, flying squads, armed with nets and DDT, rush to the spot.

Sardinia presented a peculiar problem to the malaria fighters when they first mapped their plan of action. The island's fertile plains, where the mosquitoes were thickest, could not be sprayed with any preparation harmful to livestock. Entomologists coming to Sardinia pinned the guilt of malaria on the "fabrenchaie" species of the *Anopheles* mosquito. Then chemists developed what they called DDT-naphtha ERLAS, deadly to these mosquitoes but not dangerous to cattle and other farm animals.

—*Tropical Medicine News*, June 6 10, 1949

INDEX VOLUME VIII 1949

- Addicts, Opium, Endocarditis in, 358
 Adrenal Medulla, Pheochromocytoma of, 79
 Adrenocortical Function and its relationship to the Leukemic State, 128
 Advances in Therapeutics, 48
 Age, This, 302
 Alcoholism, Causation in 237
 Alcoholism, Seven day Cure for, 233
 Aminacoyl, (P A S), 215
 Amino Acid and Energy Utilization, 242
 Aminoacids in deafness, 20
 Anaemias in Pregnancy, 333
 Anaemias of the Newborn, Diagnosis and Treatment of, 74
 Anaemias pernicious, vit B₁₂, Therapy 175, 176
 Analgesic Drugs, 354
 Androgen Therapy, 350
 Androgenic and Estrogenic Smears of Fetal Sex, 248
 Anesthesia and Surgerv, Cardiac Patient for, 99
 Angina Pectoris, Vitamin E in, 273
 Annual, Medical, (1948), 48
 Antihistaminic Drugs in Dermatology 205
 Antimony gluconate, 4
 Atomic Energy Commission, medical program, 124
 Aorta, Coarction of, 245
 Arrhythmias, Acute, Intravenous Quinidine in, 357
 Cardiac, Effects of Atabrine on, 132
 Arterial Disease Nail Changes in, 107
 Peripheral, 107
 Arteriography, Retrograde in Cardiovascular Lesions, 240
 Arthritis, Rheumatoid, Gold Compounds in the Treatment of, 120
 Tissue Examination in 131
 Asthma, Bronchial, Intravenous Oxygen in, 125
 Atabrine Effects of on Cardiac Arrhythmias, 192
 Athle, L H, 65
 Atomic Energy Commission, Medical Program of, 124
 Atrial Septal Defect, 81
 Aureomycin, 68
 Aureomycin Therapy in Human Brucellosis, 127
 Auricular Fibrillation, Study of 102 Cases, 313
 Auricular Paroxysmal Tachycardia, 203
 B₁₂ Vitamin in System disease, 101, 110
 Bacteriology, Text Book of, 214
 Bacitracin in Surgical Infections, 211
 Baliga, A V, 6, 7
 Banker, D D, 111, 296
 B C G Vaccination, 10
 Bharucha, E P, 113
 Book-reviews and Notices, 48-103 135, 184, 214
 All-India Medical Directory, 184
 The Conquest of Tuberculosis, 130
 Ectopic Pregnancy, 280
 Illustrative Electrocardiography, 49
 Indian Heart Journal, 135
 Intern Jour of sexology, 104
 J of Guj Research Society, 48
 Medical Annual, 48
 Pulmonary Tuberculosis, 48
 Recent advances in Therapeutics, 184
 Symposium de hematologia, 135
 Text-Book of Bacteriology, 214
 Year Book of Pediatrics, 103
 Year Book of Endocrinology and Metabolism, 104
 Bhende, Y M, 111, 206
 Bite of Spiders, Calcium Gluconate in, 180
 Blood Flow in Man, Hepatic, 270
 Radiocine in, 335
 Transfusions, Hemosiderosis Aggravated by, 359
 Tumours, Nitrogen Mustard Therapy in, 69
 Brain, Hypertension and Tachycardia due to Concussion of the, 278
 Brucellosis, Human, Aureomycin Therapy in, 127
 Bulbar Palsy, Malignant Hypertension, Hyperthyroidism and, 88
 Calcium Gluconate in the Bite of Spiders, 180
 Cancer, Hormonal Treatment of, 133
 Carcinoma, Gastric, Detection of, 275
 Of the Prostate, 210
 Of Stomach, 244
 Cardiac Diagnosis, Pitfalls in, 343
 Cardiac Failure, Congestive, or Myocardiac Insufficiency in India, 281
 Patient for Anesthesia and Surgery, 99
 Cardiovascular Rejection, 309
 Cerebellar Tumour, 6
 Chitre, R G, 113, 258
 Chloromycetin, 77, 141
 in Enteric Fever, 185
 in Typhoid Fever, 192
 Choroid, Rupture of the, 310
 Coarction of Aorta, Surgical Treatment and Physiopathology of, 245
 Congestive cardiac Failure, 281
 Coronary Vasodilator Action of Khellin, 353
 Curare and Prostigmine on the C. N. S., Effects of, 130
 Deafness, treatment with vitamins and aminoacids, 20
 Death of Swami Vivekananda Thy Neighbour, 105
 Deficiencies in Pregnancy, 94